Shaping genes : ethics, law, and science of using new genetic technology in medicine and agriculture / Darryl R.J. Macer.

Shaping Genes

Ethics, Law and Science of Using Genetic Technology in Medicine and Agriculture

Darryl R. J. Macer

Shaping Genes is an important new title for all people working in Science, Health, Law, Bioethics, Biobusiness, Public Policy, Students and Interested Public.

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Darryl Macer obtained his Ph.D. at the Medical Research Council Laboratory of Molecular Biology, Cambridge, England. He conducted research in bioethics at Trinity College, Cambridge University, England during 1988-1989. He is a consultant to the New Zealand Department of Scientific and Industrial Research and the Ministry for the Environment. He is a Foreign Professor at the Institute of Biological Sciences, University of Tsukuba, Japan, and continues to research the ethical, legal and social implications of the use of new genetic technology.

Eubios Ethics Institute

ISBN 0-908897-

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Ethics, Law and Science of Using New Genetic Technology in Medicine and Agriculture

Darryl R. J. Macer, Ph.D.

Eubios Ethics Institute 1990

Eubios Ethics Institute
Christchurch Tsukuba

The Eubios Ethics Institute is a Nonprofit Group that aims to stimulate the discussion of ethical issues, and how we may use new technology in ways consistent with "good life". An important part of this dialogue is to function as an information source for those with similar concerns.

National Library of New Zealand
Cataloging-in-Publication data

Macer, Darryl R. J. (Darryl Raymund Johnson), 1962-
Shaping Genes : ethics, law and science of using new genetic technology in medicine and agriculture / Darryl R.J. Macer.
Christchurch, N.Z. : Eubios Ethics Institute, 1990.
1 v.
Includes bibliographical references and index.
ISBN 0-908897-00-6
1. Genetic Engineering--Moral and ethical aspects. 2. Biotechnology--Moral and ethical aspects. 3. Bioethics. I. Eubios Ethics Institute. II. Title.
174.9574

Key Words: Animal Rights, Bioethics, Birth Control, Embryo Research, Eugenics, Field Release of GMOs, Genetic Counseling, Genetic Engineering, Genetic Intervention, Genetic Screening, Genetic Therapy, Genetically Modified Organisms, Hippocrates, Human Genome Project, Medical Ethics, Patenting of Life, Reproductive Technology, Risk Evaluation, Sex selection, Sustainable Agriculture.

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Shaping Genes

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Preface

I hope that this book is able to provide up-to-date science with some illustrations of the ethical dilemmas that arise from the use of new genetic techniques. It is intended for all students, researchers,practitioners and public interested in these issues, to contribute something to the ongoing discussion of bioethics. The book has been written with an extensive bibliography so that it can be used as a source book for others directly involved with, and researching these issues, who may come to different conclusions.

This book considers the problems for the use of new genetic and reproductive techniques in medicine, together with the use of genetic engineering for nonhuman applications. This includes such issues as environmental ethics and regulations, commercialisation of science, and the use of animals, with the subsequent ethical, legal and social problems. The reason for the combined approach is twofold, one is the genetic technology is applicable to all organisms, and the second is that bioethics should be viewed as the study of life in general. It is impossible to separate many people's apprehension to genetics from the feared abuses of human applications, such as the eugenic extremes of the past, despite the moral gulf between medicine and plant breeding. Agriculture can be argued to be even more basic to life than medicine, and if we upset the environment it is more catastrophic than the absence of a new medical treatment. I would appreciate any feedback and criticism of this work, as these issues require continued development and discussion.

I would like to thank many people for supporting this work. I thank Trinity College, Cambridge, England, for financial support that they provided during 1988 and 1989, and the use of facilities at the University of Cambridge. I thank the staff of the Hastings Center for time spent there. I thank the New Zealand Department of Scientific and Industrial Research Crop Research Division for support given to enable further research into ethical problems in the area of nonhuman applications during the first half of 1990. I also thank them for permission to quote from their New Zealand public opinion survey. I wish to thank all the people who provided me with important information to be used in this book, without whose help it would be diminished. I am obliged to the critical comments made on different parts of early drafts of this project, by the following people; Rev. Michael Banner, Prof. Sam R.J. Berry, Mr Howard Bezar, Prof. John W. Bowker, Prof. Alastair V. Campbell, Dr. Tony Connor, Dr. Tim R. Forester, Dr. Neil Hartman, Mr. Sean Jackson, Prof. D.Gareth Jones, Dr. Tit Meng Lim, Mr. Keith Moyse, and Rev. Melvin Tinker. I am indebted to the support given by my wife Nobuko, and our parents, in this project. I am responsible for all the inadequacies of this book, and look forward to receiving criticism of it.

Darryl Macer
Institute of Biological Sciences
University of Tsukuba
Tsukuba, Ibaraki 305
Japan.
September 1990

1. Is There A Problem?

New Technology

There have recently been major advances taking place in medical science and genetic technology. The growing and widespread availability of such advances has greatly increased the real and potential impact of genetics on the world. We are living in a revolution, in biotechnology and biomedicine. This raises urgent ethical questions. I attempt to examine some of these questions in this work, and examine the types of questions which need to be asked.

There have been several books written recently which claim that we need very new ideas and approaches in ethics to deal with the novelty of the new genetic techniques. Some advocate a radical shift in the basis of our ethics to deal with these problems, such as a move to Eastern religions (Suzuki & Knudtson 1989). Others appear to be so afraid of the possibilities that they want us to avoid using these technologies (Rifkin 1983). There has been a wide spectrum of objections to the new technology, claiming that it poses new and much greater problems for humanity and the world than previous technologies. The new genetic technologies are portrayed as likely to lead to a catastrophe if they are not severely restricted or stopped. However, what I intend to show is that although this new technology has a few novel features, other technologies are also associated with similar ethical problems, and the uses of the new genetic technologies can be assessed by similar principles of ethics. In fact, I regard genetic engineering as a catalyst for our thinking about life itself.

We will examine the details of the new technologies, with an up-to-date account of the progress in each area. Genetic technology consists of the theoretical basic research in genetics aimed at acquiring scientific knowledge, and the applied research. Many possibilities that were classed as speculative several years ago are now grounded on experimental results, and have been applied. We can genetically analyse DNA from a single cell, and babies have been born from the preimplantation diagnosis of early embryos. We can make faster growing fish and pigs, crops resistant to insect attack, or tomatoes that stay firm. We have begun to insert genes into human beings. The progress should continue to accelerate. We should consider what special characteristics of the new technologies is considered to be so awe-inspiring and what features they challenge. We need to examine the validity of claims made and what ethical principles we need.

It is a common belief that scientists do not have any interest in ethical standards, and are uncaring about the social implications of their work. However, some of the major ethical debates over the uses of technology have been begun by scientists themselves, such as that among physicists about the development of nuclear weapons, or among geneticists on the perils of transforming DNA. Some scientists do care about the social, moral and legal aspects of their fields of study. A basis for our ethical stance in areas concerning the use of genetic technology should

be firmly grounded in biological knowledge, as a clear knowledge of the scientific facts is essential to any discussion of moral issues. This means the education of society on the likely uses of genetic technology in the immediate future, and the possible uses in the long term.

Molecular biology has moved so fast in the last few years that even those in the field find it difficult to keep up. In some small way, I hope that this book can aid those who cannot spend their days in the library to watch for news outside of their immediate research interest. Science, as viewed by the public, may have ended being the never-ending search for truth, and begun to be the craft of the manipulation, modification, substitution and deflection of the forces of nature. Pure science does still exists, but much emphasis is given to "engineering".

Biology itself is not competent to adjudicate on matters which are philosophical and ethical, such as the status of the human fetus, the use of genetic screening or engineering. The good things we can do are only made complete by the things we refuse to do. People may voice concern, but in the application of scientific techniques, if the line of refusal is not drawn before any violations, it is no longer civilised technology. Our ethics must be more than a rationalisation for things that we are bound to do because of interventions science has now made possible. The onus is on the scientists and technologists to prove beyond reasonable doubt that any real risks can be managed. The increasing understanding of recombinant DNA technology is revealing areas in which caution must be applied, and it is also showing areas where there are few risks. We must also consider the way society has handled similar issues in the past.

Just values of society should be used to assess the medical-technical possibilities that are occurring. We should not change our basic morals because of the possibilities offered by new technology: what we may have to do is to extend their application. We do need however to be open to change our attitudes and realise that technological changes are not necessarily changing our standards, but are accepting new solutions to biomedical problems. There is a major challenge to our medical ethical system from these new techniques, as they could lead to the management and control of parts of human life from conception to death.

The interventions planned in the sphere of genetic technology will affect not just ourselves, in medical uses, but our agriculture, microorganisms, plants, animals and possibly entire ecosystems. Such an increase in our ability to change lifeforms in biology, and especially medicine, and the moral issues attendant upon them, is reflected in the concentration of attention which has given birth to the newly-described science of "bioethics". *Bioethics* is a composite term derived from the Greek words for life, *bios* and ethics, *ethike.* It can be defined as the systematic study of human conduct in the area of the life sciences and health care, in so far as this conduct is examined in the light of moral values and principles. The subject of bioethics has been highlighted by questions in the area of health care. Health policies should be directed to applications of medical knowledge that relieve and prevent human suffering or protect and promote human life.

Ethics has been described as the science of morals, and the rules of conduct recognised in human life. The rules of conduct must be essentially social: they apply to individuals living together in a society. The view of "society" includes many people's outlook, and there are deep political and ideological rifts which exist within humankind,which continue to result in antagonisms and rivalries between

nations. The views of religious people are very important because 90% of the world's population are at least nominally religious. Within religions there is also division on many issues on how to act, especially in unforseen or unprecedented issues. Academic philosophers and scientists need to remember that their world view is not the predominant view of life, and it may not even be understood by a lot of people. We need to work towards a few general ethical principles that can be applied by the majority of peoples of the world in a fair, just and useful way.

We need to look at the existing ethical traditions and attitudes that affect the use of new genetics. Since many of the concerns involve medical matters, medical ethics is a key issue. Standards governing the practice of medicine have arisen as a result of continual interactions at the level of the perception and propagation of world-views by groups in society intending to maintain or establish social order and the interactions between individuals physicians and their clients. We can define "morals" as judgements on individual activity, "values" as stated expressions of the cultural framework within which these judgements are made,and "ethics" as socially derived generalizations induced from individual morality. Medical ethics continues to develop, and has important features to learn from challenges discussed later.

The Gene Scare

There have been diverse public concerns expressed over the use of new biological technologies. While those technologies include a wide range of techniques, and may be called biotechnology, the expression "genetic engineering" is probably better understood but causes the most emotional response. Many people can not distinguish genetic engineering from other techniques, and in fact may not be sure what the term means. A simple definition would be that genetic engineering encompasses those techniques that manipulate genes, especially those using recombinant DNA techniques. The purpose of genetic engineering is to introduce, delete or enhance a particular trait in an organism. This is achieved by either inserting foreign genes, or by altering the existing genetic make-up of the organism. It may involve replacing a single DNA nucleotide, or multiple genes which are thousands of nucleotides in length. Genetic engineering is only part of biotechnology. Biotechnology could be called the use or development of techniques using organisms (or parts of organisms) to provide or improve goods or services. Biotechnology itself is part of an expanding technology based on a long foundation of human use of living organisms.

This book seeks to examine public concerns about genetic engineering, and responses to them. To gain understanding of what people want, and to understand their fears, we need to look at public opinion. Some of the concerns have little factual basis, but may require public education to dismiss. Responses to these concerns involve both philosophical argument and understanding of current scientific knowledge. Concerns which are genuinely important are highlighted.

There are arguments that are commonly used in support or against genetic engineering. It is important to briefly survey these arguments, and then to examine them to see what are the key factors. In favour of genetic engineering is utilitarian thinking. There will be risks for individuals, but the goal of the application of these techniques includes benefits to human beings and the environment. We are rational

beings and we should take advantage of the chances used to apply our rationality to improve agriculture. Against genetic engineering are arguments such as it is unnatural. The most dramatic of these concerns are that we will replace natural procreation of human beings with extensive genetic selection of fetuses. We will always be unsure of the long-term affects of our manipulations, and will have doubts as to their safety. We are still ignorant of the mechanism of gene action, and living systems are very complex. The misuses of genetics in the past, illustrated how bad values may be propagated, and these techniques could be abused in the future. There may be more important uses to put our resources into than into genetic engineering. Although much work in genetic engineering has involved microorganisms and recently plants and animals, much of the anxiety concerns extrapolations to humans. All of nature is important, especially with an ecological awareness, but because of the fears relating to humans they are highlighted.

We need to question what is the goal of society. For several decades after World War II there was a feeling that science and technology could provide everything, and they should be promoted. A majority saw that only science based technology could change our society for the better. However, during the last two decades there has been a growing feeling that technology has actually led to many problems as well as benefits. There has been a growing and strong anti-technology feeling (not so much a anti-science feeling) (Cavalieri 1985). There is still a majority public support for science in most countries, but it is mixed with concerns.

Scientists assume that science is naturally good for society, but this is not an unconditional assumption. We could remember the parallel made between biotechnology and computers, both are thought to give rise to major changes in society, and they are both having some impact. In the early days of the computer revolution the computer was going to change radically every aspect of human life, if some people were listened too. However, today we do not hear so much about this, though I doubt it is because it has lost its potential power for change, but rather that society has accepted the changes so far, which for most people have been for the better. However, with biotechnology we are dealing with the complexity of life itself, which may have greater potential. It has also begun, and society is accepting it and society will continue to change. There is a need for more consideration of the way in which society changes, what effects there are on family life and whether they are for the better or not.

We are often uncertain of the precise outcome of interventions in nature or medicine. Fortunately we are more ready to admit that uncertainty today than in the past. While being the norm in medicine for millenia, has taken recent major ecological disasters, some that have been growing for over a century, to convince people that industry or agriculture may have bad consequences. We will never be certain to have complete control over the effects of introducing new gene sequences. Much further experimentation will be required before we will be able to ethically use genetic therapy, except for otherwise untreatable diseases. Ignorance of the consequences necessitates caution in using new techniques, and this is an approach seen in the regulations governing the introduction of genetically engineered organisms into the environment, and in the use of human gene therapy. Researchers need to consider adverse public reaction to the production of genetically-modified organisms (GMOs). Public opposition to field testing of GMOs is a concern as there have been incidents in the USA and in Europe of both legal prohibitions such

as court-orders to prevent trials, and of illegal destruction of trials and property involved.

The uncertainty is all the more important because of the major consequences of any disaster. If we introduce very different gene combinations into the environment they could have major consequences, which may be irreversible. The new genes may enter other organisms, or the new organisms themselves may replace existing organisms in the ecosystem. The ecological system is very complex, minor alterations in one organism have effects throughout the ecosystem. We can not yet predict these affects, therefore we must be careful, and move cautiously. We have had bad experiences in the past to make us realise our limitations. There is only one earth and we are dependent upon it, we must walk carefully. There have been many examples of technology that have exploited nature and natural resources. We are still in a crisis regarding the environment and what we have done, and it is finally becoming a major issue now that such major signs have become apparent to people. Even if the motivation is to save our own skin at least something may be done when people become aware of the dangers.

From an ethical point of view it is also essential to respect nature. We are causing the extinction of numerous species, and causing large imbalances in food chains of organisms that we use for food, such as animals. There are a mixture of concerns, from the level of protecting species diversity itself, another is farming methods we use for animals. Genetic engineering could have varying affects on this problem. It is often claimed that it will revitalise agriculture and increase food production. Some see it as a new way to generate large quantities of renewable resources, using the energy of the sun, to generate biomass. Maybe it will, but we must be careful that we do not disturb the balances of nature so much as to cause more damage than good.

It has been claimed that genetic engineering is like nuclear science, as both confer a power on humans for which they are psychologically and morally unprepared (Cavalieri 1985). Certainly biologists claim that they can outdo evolution, and use genetic engineering widely; but the question is whether we are ready for this new power. In the 1940's we learnt how to use nuclear fission, and physicists initially motivated by the aim of developing a weapon to use on fascist Germany, became so wound up in their work that they did not slow down when they knew it would not be needed. After our experience with atomic power we should face the biological revolution with our eye's open, another question is whether we do?

Another question is, in whose hands will the power be, with the scientists or under commercial control. While scientists might be able to retain control initially, it is very likely that similar to all developments involving much commercial interest, the commercial interest will dominate. Much of the research in these areas is paid for by commercial companies, even human gene therapy has commercial backers. Medicine is very big business, as we already know from the huge number of duplicate drugs and the pharmaceutical companies. Genetic screening tests are being commercially sold, though there is actually little profit in genetic screening. In agriculture also, with many seed companies and the major herbicide and pesticide companies have developed new GMOs. There is much government involvement at this early stage in controlling the trials, but governments are also keen on developing

new money earners. On the positive side, because of the lack of biological knowledge, some commercial companies have been forced to conduct much basic research, before the technology can be fully exploited the details of gene regulation need to be known.

In a lot of countries there has been considerable investment in genetic engineering, reflecting world-wide interest in the technology. The level of investment world-wide is unusual, given that large amounts of research are needed before any product is produced. The potential of biotechnology is very wide. In 1987 there were 400 biotechnology companies in the USA, and another 70 established corporations with significant investments in it. The combined U.S. industry is spending over US$ 2 billion dollars annually in biotechnology, with a similar amount being invested in public money. There are hundreds of international companies, especially in Japan and Europe. Biotechnology is a tool for a wide variety of industries, and it is difficult to imagine all the fields which it will touch. Genetic engineering is also used in many industries, agriculture and medicine, and scientific research.

Outline

This book considers a variety of specific areas of concern, and suggests approaches for dealing with them. Throughout the book ethical questions which are associated with different techniques are discussed. The book is divided into four sections, and sixteen chapters, including the first one you are reading. The introductory section of the book considers a background, to the problems, and a background discussion of the techniques of genetic manipulation. The second section considers some key ethical concerns, and discusses them in four chapters. The third section considers nonhuman genetic intervention, the applications of genetic engineering to make GMOs, and the environmental safety of their release. The regulations to deal with these issues are assessed, and the influence of commercialisation is addressed. The fourth section considers human reproduction, the new reproductive techniques and the use of human genetics. I will give a deeper outline in the following pages.

The second chapter describes some of the techniques involved in genetic manipulation with examples illustrating the reasons why this technology is being used. There have been other books providing more detailed descriptions of the workings of the cell and genes, the purpose of this chapter is to provide the reader with the basics that are needed to consider the applications described in following chapters.

The third chapter considers general ethical concerns, such as our use/misuse of nature. The broad range of genetic engineering has been associated with what has been called the "*Frankenstein Factor*". Others accuse genetic engineers of "*Playing God*", or "*Interfering with Nature*". People are also concerned about moving genes between species, or the integrity of species. Part of this concern is a reaction against the rapidity of technological change, with a perceived harm to society values, and part a reaction to damage caused by other technology in the past.

Other concerns are those of the "*slippery slope*" type. There is a lack of trust about whether scientists can draw the line between the types of genes that are

transferred. Most important is the possible extension of techniques to humans for eugenics. The difference between serious genetic disease and nondisease characters. There is concern over how far we pursue efficiency and the limits of developing a "perfect" animal. Biological warfare is another concern. Public attitudes depend on education, however, even among educated people there is a distrust of scientists. This distrust is heightened if there is seen to be a lack of public review, or of adequate public safeguards and regulations.

The fourth chapter provides a historical and cross cultural account of medical ethics. The healing situation requires special morals as it involves a sick, vulnerable person with a healer who is required to help without exploiting the vulnerability of the patient. One method of controlling behaviour was the following of ethical codes and the taking of Oaths. There are various ancient oaths that have been discovered in different cultures, the most universally honoured is the Oath of Hippocrates. This chapter looks at the Hippocratic tradition, and why it was adopted instead of other alternatives. It provides a background for the concluding chapter, and is aimed at those with an interest in medical issues. The new genetic techniques made the patient-health care provider relationship become even more important, and we must examine how to ensure patient's autonomy is respected.

In the fifth chapter the status of the human embryo is discussed. It is a key question in several important issues of reproductive technology, both old and new. There are questions of abortion and fetal tissue transplants. After discussing the ethical status of the embryo at different stages in development, we can then consider the question of embryo research. This is a very contentious area and different countries have divergent legislation. Legislation needs to include new techniques such as developmental studies on human embryonic carcinoma cell lines.

In the sixth chapter the contentious issue of animal rights is discussed. Religious and philosophical views are contrasted. We can ask in what way will genetic engineering challenge our thinking, and challenge our standards for animal care. The creation of very diseased animals as models of human disease is addressed. There are concerns for animal welfare in the production of new strains of diseased or unusual animals, such as "oncomouse" which is used as a probe for cancer. There are attempts to make faster growing animals, which will go beyond the use of hormones, and battery farming as methods of making more efficient (judged in terms of profit) meat and milk. There are ethical limits to using animals in our pursuit of more profitable farming, though it does not mean we should not use genetic engineering in some way. Animals used as bioreactors can be seen as a new idea, if we forget the use of animals to produce milk, eggs or wool.

Before considering these risks and responses to public concerns, some applications using genetic engineering will be summarised in the seventh chapter. The chapter presents an overview of recent advances in different areas. No doubt there will be future additions, but there are already many applications. Like other fields of technology, potential benefits are associated with potential risks. Standards that are appropriate for use in a developed country may be unenforceable in developing countries, who may more urgently require the benefits of biotechnology.

The safety standards of genetic engineering laboratories developed over the past 15 years have been based on containment of GMOs. However, during the past decade there have been a growing numbers of cases of deliberate free release of

GMOs. As there is a lack of a predictive ecology, people are concerned about unpredictable disruption to the ecosystem. This is complicated by the possible transfer of novel genes to other species, such as acquisition of herbicide resistance by weeds. The use of monocrop systems, whether or not they are GMOs, can result in a loss of biological diversity. There is also the question of liability for harm to the environment. In chapter eight the environmental safety of genetic engineering is discussed.

The ninth chapter considers the types of regulations that are being used, and how we should regulate the release of GMOs. Comparison of international regulations is made, including guidelines developed during 1990 in Britain, Germany and Japan. This chapter also considers the pressing issue of food safety. How do we ensure that new foodstuffs made using these techniques are safe to eat?

The commercial interests in biotechnology are the subject of the tenth chapter, they concern both nonhuman and medical uses of biotechnology. Public distrust is also heightened by the commercialisation of biotechnology which may mean financial interests come first. It follows that there is a fear of large corporate control. There have also been losses to the Third World of germplasm which is the new currency of the biotechnology business. Many people object to further control by megacompanies. At a practical level this is perceived to make farmers more dependent on corporations who produce new varieties of enhanced organisms. This cannot be blamed on the science, but rather on the way it is applied, with much research being sold to corporations by the scientists who developed it, or through the way that research is funded. The patenting of living organisms is a sensitive public issue, particularly when applied to animals.

The next section of the book is the largest, and it considers the medical issues, beginning in the eleventh chapter with general interventions in human reproduction. There are issues such as the use of birth control to control the quantity of children, and also the new approaches to aiding infertility. There is often moral objection seen in the trends in emphasis from procreation to the manufacture of our progeny, and the moves away from the integrity of marriage and the family and respect for individual human life. We may need to limit the use of these technologies to people who actually require them, and to those which retain the ideal of the family.

In the twelfth chapter eugenics is addressed considering the history and current trends. We need to learn the lessons from the misuse of genetics in the past, and contrast that to the current genetic programs. In the thirteenth chapter genetic screening, from sex selection to serious diseases, and the question of the use of genetic information is addressed. The protection of patient confidentiality is highlighted in the question of the privacy of genetic information.

In the fourteenth chapter the new medical therapy called gene therapy is discussed, for the cases involving somatic cell therapy - that is where only the individual is affected. There have been approved trials of somatic cell gene insertion in the USA, and we are on the verge of a new therapy being introduced.

In the fifteenth chapter questions of positive genetic manipulation are considered. This includes embryo splitting or cloning, germline gene therapy, and the future developments with the human genome project. We need to talk about the positive genetic selection, it is already possible using artificial insemination from selected donors, and the techniques for genetic manipulation will become safe in the future. The question is so major that widespread international public discussion is

required.

The final chapter considers how the problems raised by the use of new genetic technology can be dealt with using principles developed in bioethics. There are ethical problems in the practice of human genetics, which are encountered in the everyday operation of medicine. There are social-ethical issues of genetics when applied to medicine or agriculture. There are new social alternatives and policy choices arising from the impacts of genetics on society. We must discuss how we may best move to sustainable living. A way of living with the rest of humanity and nature, that will be sustainable for the future. Clarification of research goals are needed, to allay public concerns about benefits to society and the environment. Researchers need to know whether the use of herbicide tolerant plants will reduce pollution by reducing or shifting the pattern of herbicide use. Similar questions apply to insecticide and fertiliser use.

After the consideration of technological advances and dilemmas we will be in a better position to answer these questions. During the course of the discussion in the rest of the book, ethical principles have been mentioned, it is in the concluding chapter that they come together. Principles that can be applied to new situations that arise with the use of future technology are summarised. Our approach to ethics should be to learn and develop ethical principles that can cope with our dilemmas we face. It is good to ask what we can learn from the situations using genetic technology that helps us develop our medical ethics in general. The relationship between problems and solutions is interactive. There is a short summary of important conclusions that have come from the discussions in the rest of the book.

I have tried to limit the use of technical terms,while explaining as each issue is discussed, the necessary biology required to understand the issues involved. The science referred to is based only on that already experimentally performed, and the likely practical extensions. There have been exaggerations used by many writers. In fact, the science already performed is mind-boggling in its capability: there is no need to become fanciful. I include recent references which I hope may aid others to review the new genetics and offer their approach. I have included authors names in brackets in the text, in preference to a numbering system. This will be familiar to scientists, and it may alleviate some of the need to constantly refer to footnotes.

Everyone should form an educated opinion on these moral problems, not just the scientists. All people, creators of technology and users of it, are responsible for their actions. Science is one of the most powerful agents of change in society, and society should learn how to handle it. There will need to be more public education of science, and the issues raised, to make this possible. Bioethics is not concerned with a philosophical justification for a secular pluralist morality, but with where we must draw the line between doing an experiment, or not; between applying technology or not. The proper limits for science should be governed by morality.

This revolution has more consequences for human life than the Copernican or Darwinian or Technological revolutions. We can control a lot of diseases, and we can reflect on deficiencies in our own genetic make-up in the fields of genetic manipulation, gene therapy and quality control. There are questions about the status of marriage and family life, the degree of freedom human beings should have to procreate and chose a mate, and/or child, the status of human embryos and the selection of embryos to be aborted. I will now begin to consider a few of these.

2. Genes and Life

The Advent of Molecular Biology

Our first reaction to the great advances in science, and in the field of genetics, should be admiration (Haring 1975). The more we understand the language and message of the genes in humans and other creatures, the more we can come to understand our history, and understand better our unique position as living creatures. Man alone, has gained the ability to adapt our environment to our genes, and is learning how to adapt our genes to the environment. At the same time we appreciate the universality of the genetic code, and the implications this has for our understandings of our biological origins.

Genetics as a science could be considered to have begun with Mendel' s experiments with the passing of parental characters in peas in the middle of last century. However, the idea that characters or traits were passed from one generation to the next has been known for many millenium. The cross-breeding that produced agriculturally useful crops such as wheat or corn has a long history. So does the breeding of domestic dogs or cats from wild ancestors. The knowledge that interfamilial marriages lead to more handicapped children, and that blue eyed children come from blue-eyed parents is also very old.

Some of the ideas of how human characters were passed on are fascinating to us now, but they were commonly held beliefs for millenia before we were able to understand them. Aristotle thought that the female supplied the "matter" and the male the "motion" that would determine the child's characteristics. There are similar ideas in ancient manuscripts of other cultures also. However, Hippocrates and Galen, and Islamic writers later, thought that because both man and woman produced semen they contributed equally to the process. As it will be discussed in chapter 12, there were ancient eugenic ideas that arose specifically because of, often incomplete, knowledge. In the nineteenth century in Europe, the human genetic traits were thought to be associated with blood. There were exceptions and irregularities, such as why children could have different eye colour from their parents due to recessive alleles which were to be explained by Mendelian genetics. We now know that blue colour is recessive to brown, so that to have blue colour one must have both genes for blue, if there is just one then the eyes should be brown. There were various theories for the transmission of genes, I will not dwell on them but refer to other books (McKie 1988). The principle alternative was Lamarckism, which thought that body characters acquired during life could be passed in the genes from parents to children.

The physical location of the genes has only been determined since the beginning of this century. In 1908 the American geneticist Thomas Morgan identified the genes to be associated with parts of chromosomes. In 1911 they produced the first chromosome maps, and spent many decades working on genetic studies in fruit fly. In the 1940's Avery showed that traits could be passed from one

bacteria to another by a chemical called DNA. We will discuss DNA in the next section, and DNA is a widely known word in most languages today. It was the discovery of DNA as the physical substance of genes which could be said to be the start of molecular biology. Before that people thought proteins were the material, because of their complexity. DNA is chemically very simple compared to proteins, and people thought that the genetic store must be complex. It took another decade before all were convinced of the importance of DNA.

The structure of DNA was determined in 1953, by a group of researchers in Britain, including Watson and Crick, for which numerous accounts have been written (Watson 1968). The double helix structure is also commonly associated with the public image of DNA. The majority of the DNA in a cell takes the form of this double helix, though there are other important structural variations that are thought to be important for gene regulation. There are also larger tertiary structures formed by the DNA, and it is also associated with proteins in most cells. The discovery of how the genetic code is translated to protein sequence took another decade, and during this time the science of molecular biology matured. It has since grown so that it now pervades every part of biology, and has been applied to many areas.

DNA and Genes

Part of the aim of this book is to bring readers up-to-date on advances in genetic technology. It is intended that this is done so that people who have little background in biology can understand enough to get a clear picture of the ideas and capabilities of these techniques, without a need to understand all the details of the procedures. However, a few terms have to be defined and introduced which will aid this comprehension. This is the purpose of this section.

All organisms are constructed of one or multiple cells. The cell is the basic building block of life. Most cells can reproduce themselves, though in higher organisms some cells may be so specialised that they lose this ability, but may still be able to stay alive for the lifetime of the organism. The information for this continued survival, and for the very existence of cells, is contained in the DNA of a cell. It is the DNA which is the focus of genetic studies. What we may consider to be living organisms depends to some extent on our definition of life, a virus has DNA (or RNA) but can only reproduce using another organisms cellular system, so is not independently alive.

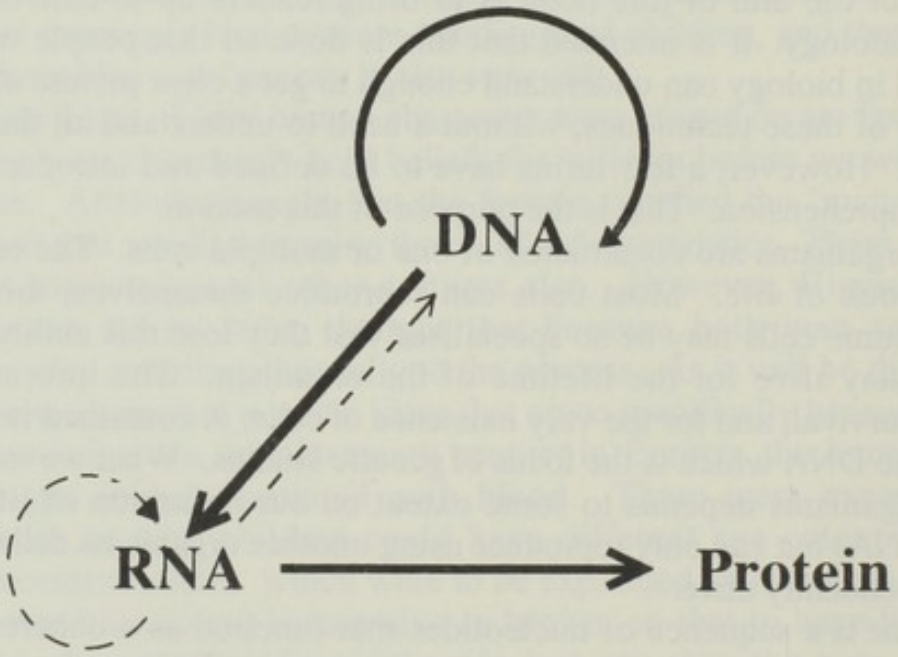
A gene is a sequence of nucleotides that function as a coherent unit. Each gene carries the instructions for a specific protein or an RNA molecule. A series of three nucleotides codes for a specific amino acid. DNA carries the information that is required by an organism. This information is translated to proteins in a sequence specific method. A sequence of nuceotides in the DNA is linearly translated into an amino acid sequence. The intermediate messenger in this process is another nucleic acid called RNA. It is not as stable as DNA, so is not used for information storage except in a few viruses. The cycle of information flow is called the central dogma of molecular biology, and is schematically represented in figure 2-1.

A typical protein consists of about 300 amino acids. The DNA needed to code for this would be about 1,000 nucleotides long. However, in higher

organisms (plants and animals) the gene on the DNA contains an alternating mixture of what are called introns and exons. The total sequence of a gene of this type may also be 1,000 nucleotides, but many are of 10,000 nuceotides in size, and the human dystrophin gene is 2 million nucleotides long! Introns contain sequence that do not code for the protein, and whose function is unknown. Exons are shorter sequences, that code for protein sequences, for example for 60 amino acid units. This process of transcription, the reading of DNA into RNA, and the splicing of the exons in the RNA together to form the messenger RNA to be used for protein synthesis, is represented in figure 2-2.

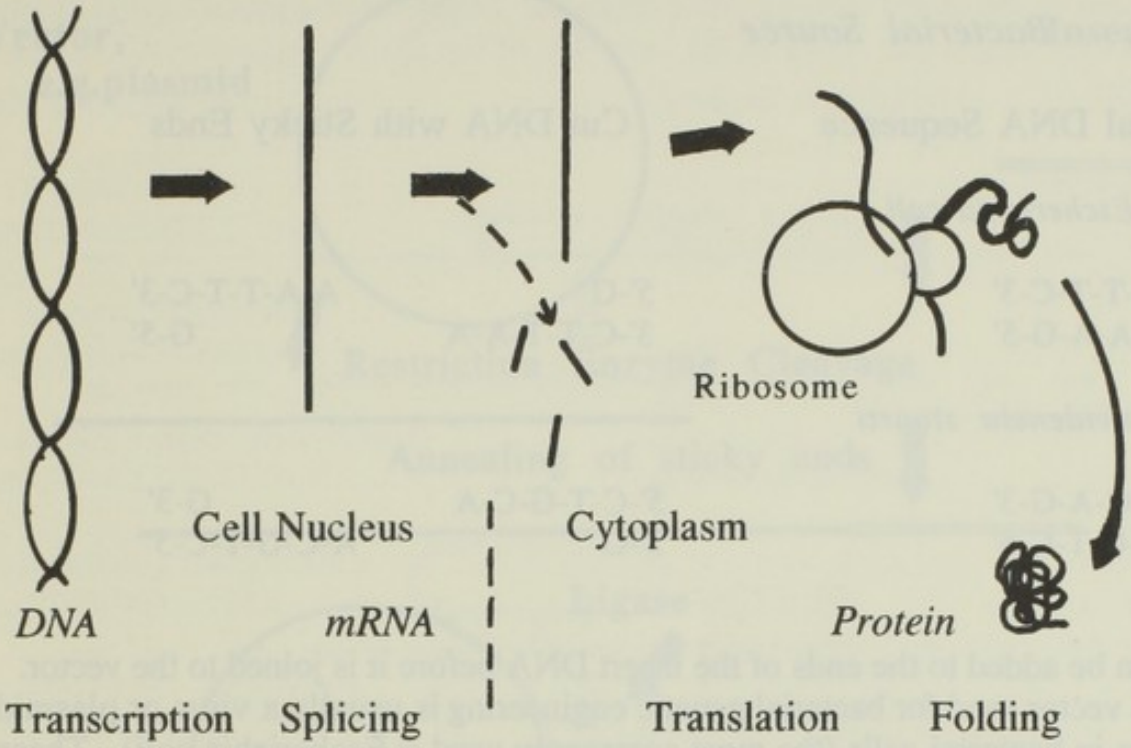
Modern genetics and molecular biology have led to techniques by which it is possible to find the exact chemical sequence of any gene from any organism. The genotype of an organism is the complete set of genes that they possess. This is determined at the time of conception for multicellular organisms, and is the same in all cells of one individual organism. Every individual of a species possesses a specific genotype, consisting of many genes. The genotype of all cells derived from the same cell will be the same, unless a mutation occurs. For sexually reproducing organisms the genotype of each new individual is different because the genes from two parents are shuffled. The phenotype of an individual is determined by the constant interaction of their genotype and the environment.

Figure 2-1: The Central Dogma. Information flow is in the direction of the arrows, the broken arrows represent special circumstances.



The key to modern genetics has been the discovery of DNA. A gene is chemically made of DNA composed of basic building units or bases which are connected in a very long linear string, in a specific sequence. There are only four types of building bases, nucleotides, but because the sequence in any gene (between 400 and 10000 bases) is very long, there are almost an infinite number of possible combinations. The four different nucleotides that make up DNA are adenosine, guanosine, thymidine and cytosine, and are often represented by the letters A, G, T, and C. The two strands of DNA are held together by bonds between the

Figure 2-2: Protein Synthesis. Proteins are made on ribosomes, by the reading of a messenger RNA (mRNA) that is transcribed from the DNA. The RNA is spliced in mammalian cells, the function of this is uncertain.



complementary bases; A binds with T, and G binds with C. The information in DNA can be represented as a long sequence of these four letters, and the two strands of the DNA have complementary sequences.

Genetic Technology

Genetic engineering is now entering its third decade of use. In 1967 an enzyme DNA-ligase was discovered which joined breaks in a DNA chain. It is now widely used to join pieces of DNA. The first artificial gene was made in 1972 by chemical synthesis. There are now automatic DNA synthesisers in most molecular biology laboratories, which are standard equipment used in making probes to be used to screen DNA. Enzymes called restriction endonucleases were found in different bacteria that cut DNA at short, specific sequences of bases. This allows DNA to be chopped into smaller pieces, and methods were used to join the ends of the desired pieces again to other DNA (See figure 2-3). The nucleotide sequence that acts as the recognition signal usually contains the specific nucleotide that the cut is made at, but for some endonucleases the cut may be made at a certain number of nucleotides further along the DNA.

Using these enzymes new pieces of DNA can be incorporated into carriers called vectors as shown in figure 2-4. To allow specific joining of the inserted DNA into the vector, the sticky ends must correspond. If the inserted DNA does not have the correct nucleotide sequence, then short synthetic nucleotide sequences, called

Figure 2-3: Restriction Enzymes Different restriction enzymes recognise specific DNA sequences, and cut or join DNA at particular nucleotides.

Enzyme, *Bacterial Source*

Original DNA Sequence	Cut DNA with Sticky Ends
Eco R1, *Escherichia coli*	
5'-G-A-A-T-T-C-3'	5'-G A-A-T-T-C-3'
3'-C-T-T-A-A-G-5'	3'-C-T-T-A-A G-5'
Pst 1, *Providencia stuarti*	
5'-C-T-G-C-A-G-3'	5'-C-T-G-C-A G-3'
3'-G-A-C-G-T-C-5'	3'-G A-C-G-T-C-5'

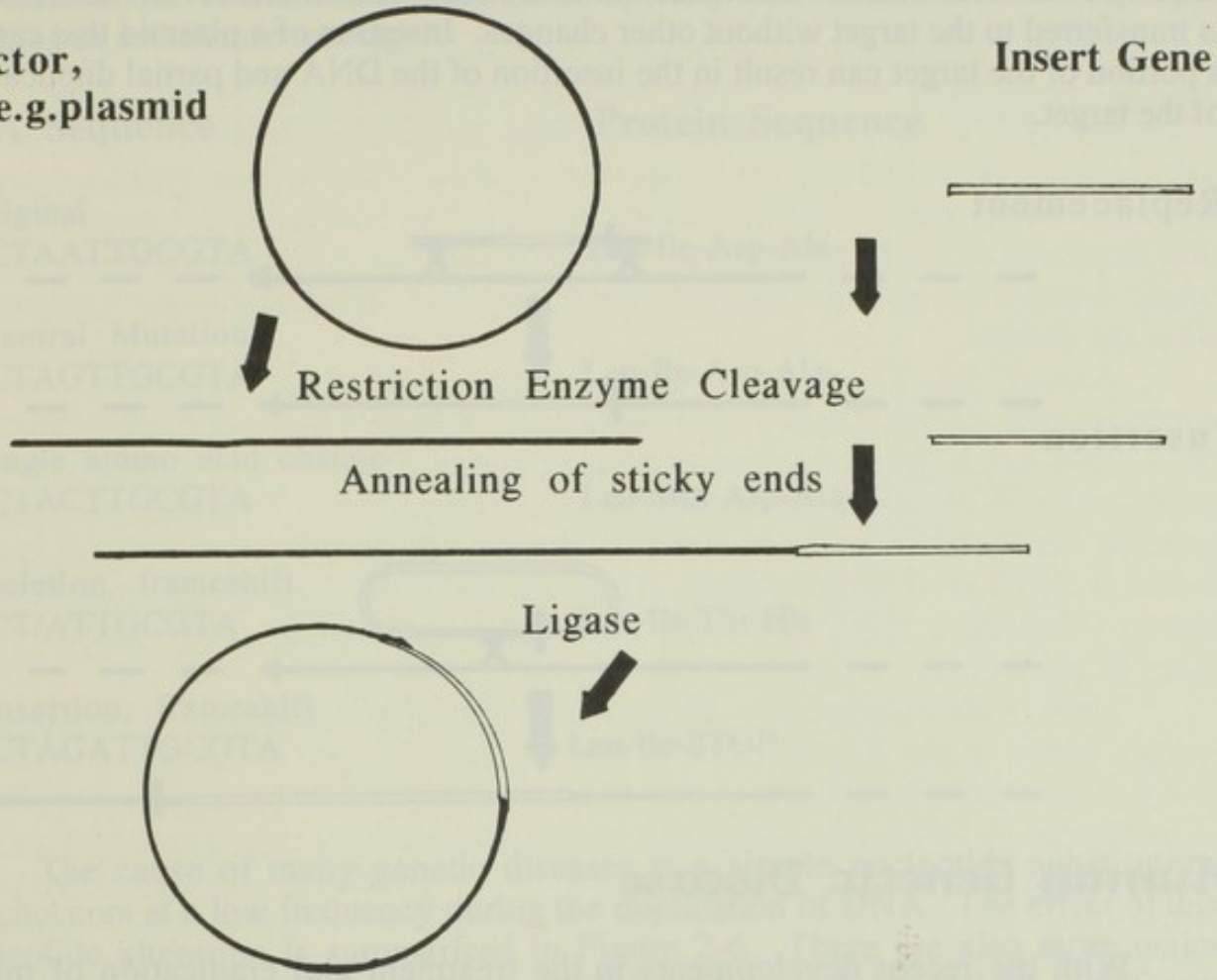
linkers, can be added to the ends of the insert DNA before it is joined to the vector.

The vector used for bacterial genetic engineering is usually a virus or plasmid that resides in bacterial cells (the most commonly used is Escherichia coli). These plasmids or viruses normally multiply in the cell, and will also do so with any inserted foreign DNA. For insertion into mammalian cells the DNA is usually incorporated into the cell's chromosomal DNA. This may occur by use of an intermediate vector such as a virus which normally inserts itself into the chromosome. Recombinant DNA technology allows the Earth's entire genetic resources to be exploited by providing a means of overcoming natural barriers of gene transfer. Though, as results of experiments have shown, some interspecies "genetic engineering" has been occuring in nature for eons, without apparent catastrophic consequences.

During 1973-1976 there was a voluntary moratorium imposed by scientists on the practise of introducing foreign DNA into bacteria. The fears were that moving genes widely could have bad consequences, for instance it could cause the spreading in the microbial world of antibiotic resistance, or toxin formation; or that genetic determinants for tumour formation or human infectious diseases would be transferred to bacterial populations, which could then infect human beings. The safety of genetic engineering is a major debate in itself, and is discussed in depth in chapter 8.

Since the decision that such experiments were safe, the technology has been extended to greatly increase the number of different vectors, so that many organisms can be "engineered", and the range of possibilities has also increased with the large number of different genes which have been identified, sequenced and isolated (Marx 1989a). The technological principles are similar for all the manipulations, some details will be given where appropriate in the discussion of some examples. I will not discuss the immeasurable benefit of the techniques themselves for biological and medical research, as these techniques are now the foundation stone of virtually all biochemistry and biological studies.

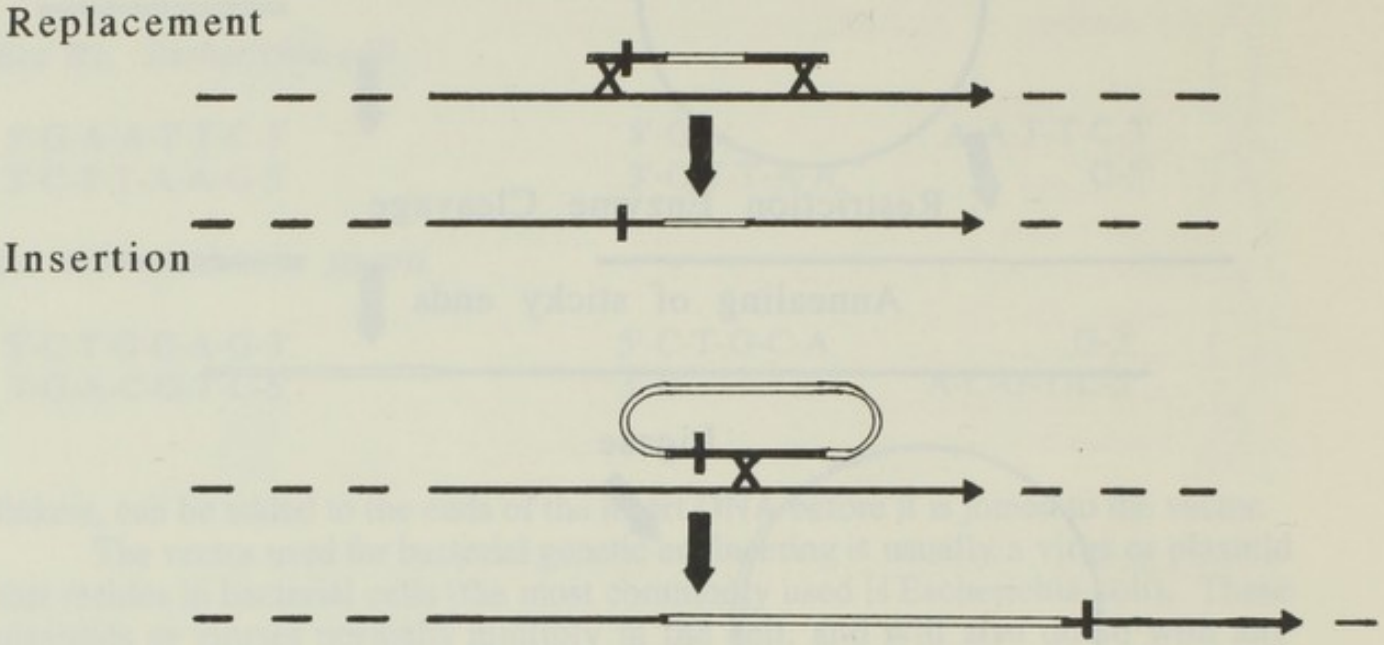
Figure 2-4: Genetic Recombination A schematic illustration of the system used for insertion of a piece of DNA into a vector, using restriction enzymes.



Many human proteins are now being commercially manufactured by use of these techniques, including blood clotting factors, interferons, lymphokines, growth hormone, erythropoietin, insulin and various growth factors, which have medical uses. Recombinant DNA techniques are also being used to produce human vaccines. Modified proteins can be made, using genetic engineering to alter the catalytic properties of natural enzymes. Many pharmaceutical products can potentially be made. The medical importance of these recombinant DNA protein products is growing, and the availability of these products makes therapies for a lot of previously untreated or uncured diseases possible. It would not be an overstatement to say that they have and are revolutionising the treatment of disease.

There are also some methods to directly insert DNA into chromosomes, using a natural phenomenon called homologous recombination. This is where matching DNA sequences match up and a break in the DNA occurs allowing insertion of the intermediate piece of DNA. The mechanics are not necessary for this chapter, what may be important is that the only foreign DNA inserted is the new insert, there may not need to be any vector DNA, such as viral sequences, inserted into the DNA. It is possible to replace a chosen nucleotide sequence with a new sequence, between the homologous nucleotide sites, which is precision genetic engineering. The procedure is schematically shown in Figure 2-5.

Figure 2-5: Gene Targeting with Homologous Recombination Two schemes of targeting are illustrated. Replacement can be made, where a portion of the input sequence interacts with the chromosomal DNA via a double crossover. Information is transferred to the target without other changes. Insertion of a plasmid that carries a portion of the target can result in the insertion of the DNA and partial duplication of the target.



Human Genetic Disease

With the recent developments in the treatment and eradication of many infectious diseases as a source of human suffering and death, the effects of genetic disease have been highlighted. Much research in medicine is being conducted in trying to understand, treat and cure some of the four thousand different known genetic diseases. Genetic disease is not usually lethal and some abnormalities have little effect. About 3% of children suffer from some type of genetic disease at birth. Every human possesses a specific genotype, consisting of many units called genes; each gene directs the manufacture in our body of a specific component, these components are usually proteins of which the most important class for genetic studies are enzymes.

There are an enormous number of genes in human beings, at least of the order of a hundred thousand different genes, and many may be involved in defining one particular function or character at the phenotypic level. As one may imagine this complex system is in delicate balance, and it only requires a defect in a single gene to disrupt this balance, the effect maybe lethal. Our genes are in long linear strings, called chromosomes. Humans possess 23 different pairs of chromosomes, a total of 46. While every human has the same set of chromosomes and thus types of genes in the same order, each gene has variant types which are called alleles. Alleles differ in their exact sequence of DNA but they perform the same function. Several hundred human genes have been isolated that have been shown to be causally related to specific genetic diseases (Davies & Robson 1987).

Figure 2-6: Mutations alter Amino Acid Sequences The original and the mutated DNA sequences may give rise to the same amino acid, a different amino acid, or stop translation. A frameshift mutation completely alters the amino acid sequence resulting in a nonsense message.

DNA Sequence	Protein Sequence
Original	
AACTAATTGCGTA	Leu-Ile-Asp-Ala-
Neutral Mutation	
AACTAGTTGCGTA	Leu-Ile-Asp-Ala-
Single amino acid change	
AACTACTTGCGTA	Leu-Met-Asp-Ala-
Deletion, frameshift	
AACT/ATTGCGTA	Leu-Ile-Thr-His-
Insertion, frameshift	
AACTAGATTGCGTA	Leu-Ile-STOP

The cause of many genetic diseases is a simple nucleotide substitution, whichoccurs at a low frequency during the duplication of DNA. The effect of this nucleotide alteration is summarised in Figure 2-6. There are also more major mutations, where large fragments of DNA can be translocated to a different chromosome. Abnormal chromosome numbers can also occur, so instead of two copies there may be three copies. Because this alters the number of alleles of genes for certain proteins, this can have major affects, usually resulting in death. Trisomy 21, where there are three copies of chromosome number 21 results in Down's syndrome, and is an example where death may not be the only result. In most other chromosome trisomies, death occurs during fetal growth, and there is spontaneous abortion.

At conception a sperm cell of the father fuses with an egg cell of the mother, this constitutes a fertilised egg. Each germ cell only has 23 chromosomes, so the fertilised ovum contains a complete set of chromosomes. This is discussed at the beginning of chapter 3 when we consider human embryonic development (Figure 3-1). These chromosomes pair up after fusion and the chromosomes of the complementary pair exchange genes resulting in an interchange of genetic information. Entirely new combinations of genes are thus made, combining different alleles of each gene in a new string, and so forming a new set of alleles in the new genotype.

Only one of each pair of alleles of each gene is needed for the normal function. Some of the alleles may be so different in their sequence from the normal that the protein or enzyme that they produce is nonfunctional. If this is the case then the individual will use the functional allele of the pair and this will normally allow a

completely normal life, or phenotype. Sometimes one of the alleles is functional not in producing the normal product but a nonfunctional product; again the individual will probably live normally. But if the individual possesses two nonfunctional, or misfunctional alleles for any gene then the effect will be a genetic disease which varies in seriousness from not being noticeable in one's life to fatality. Normally the defective allele is not used if there is a normal, functional alternative allele, and the allele would be called recessive because of this. People may carry a recessive disease-causing allele without it having any affect on them, but it is possible that it will be passed on to their offspring. In some cases the defective allele is dominant which means even an individual with one normal and one defective gene will suffer from the disease.

Among the 23 pairs of chromosomes there is a pair called the sex chromosomes, called X and Y chromosomes. A female has two X chromosomes, but a male has a mixed pair possessing both one X and a Y chromosome. The genes on the X-chromosome are dominant over those on the Y-chromosome, so if a gene on the X chromosome is defective then it will be expressed and this type of defect is called an X-linked defect. There are about 400 X-linked genetic diseases known (McKusick 1990). However 90% of the known gene mutations are on the other 22 pairs of chromosomes.

Little is known regarding the kinds and rates of mutations the occur in human beings. Much of our knowledge of genetic disease and mutations comes from the study of mutagens on animals. Animal experimentation is used to study the effects of mutagens on DNA. It is likely that most spontaneously occuring mutations are actually induced by external forces, such as ionizing radiation, ultraviolet radiation, viruses and chemicals (OTA 1986). In order to systematically detect a mutated nucleotide in DNA caused by radiation we need much more sensitive methods than are technically available now. The effect of a mutation depends on where they occur in the DNA, it can be harmless or lethal. Mutations that occur in germ cells affect future generations, but mutations that occur in somatic cells may only affect the individual. Somatic mutations play a role in the development of most cancers, being a step in the process. Mutations occuring in one generation, perhaps if due to mutagenic agents, such as radiation from an atomic bomb, or chemical agents, would continue in different ways. Any large chromosomal mutations would probably result in sterility, so would only affect the first generation after. Dominant and X-linked mutations often cause severe disease and interfere with reproduction so would not last many generations. The recessive mutations have the greatest chance of being maintained in the population, none would be eliminated in the first generation, as each individual would only be a carrier, and if only one copy, then no effect. They would be present for generations.

Genetic diseases affect all populations and were apparent before prehistory. The infant mortality rate, the number of babies dying in their first year of life per 1000 live births, in England has decreased much, from 154/1000 in 1900 to 12/1000 in 1980, but the number due to genetic disease has remained similar at about 4.5/1000 (Connor & Ferguson-Smith 1984). In fact because of advances in medical treatment there has been an increase in the number of people living to reproductive age who carry or have genes that are defective, though some sufferers do not reproduce. We all carry about twenty recessive alleles for lethal characteristics, but because these occur at low frequency the incidence of a child

Table 2-1 : Incidence of some types of genetic disease, expressed as a percentage of live births in the general population.

Disease	% Live births
Single Gene Defects	**1**
Dominant	
Retinoblastoma	0.0014
Huntington's chorea	0.01
Recessive	
Cystic fibrosis	0.04
Phenylketonuria	0.001
Homocystinuria	0.0002
Galactosemia	0.0001
X-linked	
Hemophilia A and B	0.01
Progressive Muscular Dystrophy	0.02
Chromosomal Aberrations	**0.54**
21 Trisomy	0.1
13 Trisomy	0.01
18 Trisomy	0.02
XXX	0.05
XXY	0.05
XYY	0.06
X	0.08
Complex Genetic Traits	**2**
Congenital Malformations	**1.2**
Contribution to other diseases	**?**

being born with two recessive alleles is low (Sikora 1984).

Single gene defects are the defects of immediate importance when considering the potentials of genetic therapy, although they are only one of many causes of genetic disease. 1% of live births contain known harmful gene defects, some examples are summarised in Table 2-1, and these include dominant, recessive, and X-linked defects. Many gene defects causing genetic disease are due to altered regulatory mechanisms, instead of, or as well as the production of an altered protein. In 0.5% of live births there are chromosomal aberrations, where the number of chromosomes is not 46, one of the most common and well known of these is trisomy 21 or Down's Syndrome (Jones & Bodmer 1974). Many genetic diseases (such as diabetes) are caused by multiple genes, and other diseases such as cancer are the result of environment acting upon an as yet little known genetic base. One type of cancer, retinoblastoma has been found to be caused by a single autosomal dominant mutation, and occurs at a frequency of 0.01% of births (Cavenee & Hansen 1986).

During this last decade we have discovered the mutations responsible for some important single gene diseases, such as Duschenne muscular dystrophy and cystic fibrosis. However, during the next decade there will be attention on very common diseases with complex causes including genetic elements. These include cancer, coronary heart disease, diabetes, high blood pressure, manic depression, schizophrenia, Alzheimer's disease. These are all household words, because their frequency is so high. There may be three or five genes, triggered by environmental factors, acting together. The diseases are complex, but very common. The role of diet, viral infections, smoking and other chemical exposures is unknown. Genetic susceptibility means that a particular gene is only one determinant for developing a complex disorder. In identical twin studies, if one has diabetes or schizophrenia, the other one gets it only 20-50% of the time. There have been conflicting results from gene linkage studies that have studied the disease in different families. For example there was a linkage between schizophrenia to genetic markers on chromosome 5 found by one group, but not in another family study by a different research team.

The genetic mechanism of common gene mutations is still to be determined, and there may be different types. In thalassemia and hemophilia A it is likely that there is a hotspot, where mutation can occur more frequently in the DNA. In some hemoglobinpathies there appears to have been positive selection for some alleles because of heterozygote advantage. There are some genetic diseases that have very common occurrences of mutations, such as beta-thalassemia, hemophilia A, alpha-1-antitrypsin deficiency, phenylketonuria, Gaucher's disease and APRT deficiency; while there are other diseases that have rare common mutations such as Lesch-Nyhan disease, ADA deficiency, Duschenne muscular dystrophy, Blood Clotting Factor VIII deficiency and hereditary retinoblastoma. The reasons for different classes depend on the above mechanisms, and is still to be elucidated.

3. General Ethical Concerns

The Use of Nature

When people hear of the use of genetic engineering there are a variety of immediate reactions. Often people think that the techniques are wrong and they are described as "Playing God" or "Interfering with Naturee". An OTA survey of the US public found that 26% agreed strongly, and 20% agreed somewhat with the statement that "We have no business meddling with nature" (OTA 1987b). However, these concerns are usually expressed because of a misunderstanding of what is involved, and in the same survey people would support specific applications of genetic engineering who had expressed agreement with this statement. Very few people are aware of what DNA is, as surveys of the general public in major industrialised countries have shown (OTA 1987b, Newton 1989). We need to clarify these objections to see why people raise them. In order to do this it is fundamental to examine some different views of nature.

What is Nature?

We can view nature in very different ways. Nature is composed of the material world and living organisms found on it. Some view nature as being solely for man's use, others as an expendable resource that we've been given, others as unexhaustable, others as something to use and replace, others as something to look at but not to touch, others as a cosmic harmony. Nature comes in many shapes, the air we breathe, the water we drink, the sun that gives us light, and the fire that keeps us warm. There are parts of nature to use, and parts to admire, and parts that we can not use but we must still take care of. Like the care of the gardener for the prize flowers, so our attitude should be. All parts of nature are to admire, some are useful to us also. Some resources are renewing, such as water, sunlight or air. However, the quality of these resources has been altered by pollution, the water and air pollution has even altered the sunlight we receive. We will continue to receive more ultraviolet light as the ozone layer thins. Many natural systems can produce food, natural fibres for clothes and housing, which are renewable if we do not prevent their growth. We can improve the quality of these resources by technology also. Some resources are not renewable such as coal, and gas; some metals are close to exhaustion, and others are in large excess, such as uranium for nuclear power. We are part of nature and thus dependent upon it.

Different Views of Nature

The earliest testimonies of human culture worshipped the mystery of life in various ways, the earliest cultic figures from palaeolithic ages are mother figures.

The World Mother, Queen of Heaven, and Mother Earth were worshipped under many names in the Mediterranean area. The creation narratives in the Old Testament are polemics against the Canaanite matriarchical cults. Behind this symbol of the World Mother is the notion of the world as a great human being, and the human being as a little world. The pre-Aryan, Indian Jains saw the Universe as a colossal human being, the organism of the World Mother was populated by living things without number. The symbol expresses the feeling of being at one in the world, at home. The symbol of the cosmic archetypal human being was also taken up by Christianity in places, in Ephesians or Colossians the image of Christ is transformed to the head of the church, and the church as the body of Christ, applying to the redemption of the Universe. Christ will become the head of the universe

Mother Earth, is another metaphor, and is worshipped in some rituals, she is set against the Father of Heaven. This cult was also associated with the transmigration of souls and reincarnation. Mother Earth has been worshipped in many places, in America, India and in Europe, with various names. There were cults in Olympia, Delphi, Athens; in Asia Minor she was called Ishtar, Astarte or Dianna; and in Egypt, Isis. The symbol leads to a more dualistic view of the world. There are numerous other symbols that have been used, like the feast, or the dance, the theatre, as music or as play. These ideas unite the things of the world together. Another metaphor is the symbol of the world as the work of God, and just as a machine. This has led to a segregation of the divine from the world, including the world of human beings, and ultimately leads to atheism, that the world machine, and human beings, can function without God.

A Judeo-Christian view is distinct from most views of nature. There are several features of Christian theology, such as the origin of nature, and the value placed on nature by God, that lead to a different view of nature from that of secular Western thinking. Nature is created by God, nature itself is not divine but is the handiwork of the Lord. The Hebrew concept is different to other philosophies. Man does not face a world full of ambiguous and capricious gods who are alive in the objects of the natural world. Nature is not terrifying, as it is to those primitive cultures that view every act as gods response to their actions. The Bible does not discuss the method of creation, but merely says that God created the world by His Word (Gen. 1:3; John 1:3; Col. 1:16; Heb. 1:2, 11:3). The purpose of Genesis 1-3 is not to give a scientific account of the creation of the world and the rise of mankind, but to say who created the world and the roles and relationships in it. The subject and object of creation from the stand-point of people on earth is the concern of the writer. The Biblical view of the relation of man and nature is that they are both dependent on God.

To the initial reader the creation accounts in the Bible, such as in Genesis, may appear to view creation as a completed act, but it is also stresses that God's constant and loving interest in His creative work reveals Him as one who continually "makes all things new". He governs and sustains His creation (John 5:17). The created world exists both as a manifestation of his love and his intention to manifest his love within it. The created order is dependent on God for its continued existence (Col. 1:15-17) (Montefiore 1975, Linzey 1986). The creativity of God does not cease with the physical creation of the world, God continues his work through the continuing activity of mankind to whom is delegated the task of giving it order, structure and beauty. Man is God's coworker. God created all

things, so nature itself is not sacred. Man has been told to subdue, cultivate and take care of the earth, to multiply and to have dominion over the created order (Gen.1:28, 2:15). Man's role can be seen as steward and manager, the idea of dominion is such to be caring, we could be called the priest of creation (Peacocke 1979). A Christian's vocation is to continue the "good" work of creativity, as God's invitation to him; this is a huge responsibility, and demands much positive action. Man is also a moral prospector (Matt. 13:45-46). We are stewards of the earth (Gen. 1:26,28, 2:19; Psalm 8:6-8, 24:1), all things are put under our "feet" (Psalm 8:7).

The Judeo-Christian approach directly places the blame for sin and suffering in the world upon humans. The world was made good, but man chose evil. Because of our sin we have to struggle to survive, and labour and toil. There were effects upon nature from the fall of man also. A very common alternative world view is that humans are innocent, but trapped in an evil world. Many people have felt this, and it is similar to some Asian traditions that look on the visible universe as illusory or insignificant or evil. Matter is seen as relatively bad, goodness is only attributed to the spirit, and the religious task is to transcend the world. This idea is an alternative answer to the problem of good and evil. It conflicts directly with the doctrine of creation and the incarnation. The outlook has been powerful in the past, being brought to Europe at different times from the east. Some of its ideas are mixed with certain forms of Christianity, such as the view that sex is something to be disapproved of. Derrick (1972) calls this type of heresy Manichaeanism. Manichaeus lived in 3rd century Persia, and his followers influenced the Gnostics. It has long been a rival to Christianity. The idea of living in a hostile environment is very different to the sense of exile and loss coming from the fall. Creation becomes an act of wickedness. Humans should try to rise above this world and escape from it. An alternative is to try to conquer the evil world, as modern technology is often viewed as conquering nature. Another alternative is not to view the world as evil but to overstress the difference of humans to the rest of creation. This can be done in a dualistic way, judging nature as merely mechanical. This is a view encouraged by humanists. However, these are far from the Christian view and doctrine of stewardship.

Dynamic Nature

Nature has a history, a beginning, and it evolves. It changes with time, as the physical world changes, and as some organisms die and others thrive, and has done so in dramatic ways in the past. The current number of different species alive may be only one percent of the total species that have existed since the dawn of life. It is important to view nature as changing, not a fixed or static set of objects. As the individual processes of life are dynamic, so is the composite of the lifeforms. The idea of dynamism also implies a balance. This is illustrated by the words biosphere, foodwebs or ecosystem, with the largest ecosystem being nature itself. The dynamic nature is implied in the second law of thermodynamics, and in the Biblical doctrine of creation and preservation.

We could use the term "a balance of nature", as the way different species at different levels of the food web exist together. Some eating others, while others eat them, and others dependent on the modification of the environment made by another species, with competitors at every level. There is an important inbuilt tendency for species to reproduce so quickly to be able to increase their numbers, yet this does

not occur dramatically in a balanced ecosystem, in the competition for resources, the struggle for existence, each species tries to survive to reproduce. This concept is very old, it is seen in Plato's *Timaeus* who answers the question "in the likeness of what animal did the creator make the world?" with the answer that god did not make the world like any one species but rather as "one visible animal comprehending within itself all other animals of a kindred nature" (Plato I). The idea highlights how life itself is intertwined, in a web of complex relationships. There is also a continuity between inorganic and organic, ecology refers to the relationship of every organism to the environment.

At no time in the past has nature been so dynamic than today, the reason is that man is rapidly changing it. We are making many new crops, and will be using genetic manipulation to change lifeforms themselves very quickly in the next few decades. We are raising the temperature of the earth, with all the changes that brings. We are depleting the ozone layer. We are causing the extinction of thousands of species. We are adding many pollutants to the environment. Compounds like dioxin which is the most powerful poison known, and sewage which is unnatural just because of its quantity. We have synthetic compounds like plastics, chlorinated hydrocarbons, which are nonbiodegradable. We are increasing our population rapidly, which exponentially increases the problems. we can surely say that nature is dynamic, maybe too much so. We need to take stock of some old truths, and then strive to maintain nature as a caretaker not as a commodity user.

A Christian View of Stewardship

There have been a variety of views expressed about the influence of the Christian view of nature on our current ecological crisis. Some writers see the Christian idea of the domination of man over nature as a cause, however this is a misinterpretation of this idea, and it is also apparent when visiting countries from a different tradition that the same problems have arisen. There is confusion about what a Christian view of stewardship is, so I will spend two pages to describe it.

Even if nature is not divine, it has value. The value to a Christian is derivative from the fact of creation, "God saw that it was good". The heavens tell the glory of God. This is in contrast to those philosophies which see nature as evil, such as Gnostics, Manichaens, or the Indian idea of "Maya", or illusion. The Bible says that nature is real and is good. There are other ways in which the positive attitude to the material world is expressed such as in the Incarnation, where God took upon himself the conditions of material existence. Nature displays the character of God, in its goodness and strength, constancy and concern to sustain human life (Job 12:7-9; Ps. 50:6, 148:1ff; Acts 14:17, 17:27; Rom. 1:20). However, it is not a pantheistic nature, one which is divine itself. Some can start to worship nature, as god, rather than seeking through nature to find a way beyond to God, as deistic philosophy does. Love and reverence for nature are divine only derivatively, as the creation of a good God. Nature itself does not have rights, but we do have many duties to it. Nature is not a moral actor, even if it may have some freedom inherent in the way it is made. All life has value, but not all life is of equal value.

The Old Testament was written in an environment moulded by pantheistic, matriarchal and animist religions, so there is considerable weight given to the difference between God and the the world. The fertility cults of Canaan were rejected as idolatry and the transformation of god into Baal, a divine natural power,

was also blasphemous. In modern times the reverse has occured, as the exploitation of nature in Europe was justified by distinguishing between God and the world. But neither are true. God is not just the creator of the world, He is also the Spirit of the universe, indwelling in His creation. When it suits man, we try to understand God's creation as nature, so that we can exploit it in accordance with the science we discover. We need to understand this knowable, controllable and usable nature as God's creation. We must think of nature as God's creation.

Man should value nature for itself, so we should have an interest in the preservation of nature. We should not manipulate it solely to satisfy human desire. One of the important issues is the preservation of biological diversity. There are various Biblical prerogatives to suggest that this is important. One of the most famous is the story of Noah, and the preservation of domestic and wild animals and birds (Gen. 6:13-8:1). There are also chapters in the Bible like Job 38, 39 and Psalm 104 which illustrate the wonder of unusual features of nature. All of creation is blessed (Gen. 9:9-10).

There are three balanced ideas in Genesis; that man is a natural creature subject to the earth; man is radically different from other creatures, not on basis of spiritual gifts, but because of a direct and unique relationship between man and God; and that man is the only spiritual creature. Man is an integral part of nature. When all of creation was completed, God saw "everything that he had made, and behold, it was very good" (Gen. 1:31). No distinction is suggested between man and the rest of creation with respect to natural existence. Man is flesh (Hebrew "basar"), and made from the dust of the ground (Gen.2:7, 3:19), like all creatures he received his life from the breath of God (Gen.2:7, 7:15, 22), and will return to the dust (Psalm 104:29). While man has an essential identity with the world, there is also a distinction from it. A spiritual link with God is seen throughout the Bible in the use of the terms "soul" and "spirit" (Judges 14:6, 1 Sam.11:6, Ezek. 11:19, 18:3, 36:26, Psalm 103:1, Matt.16:25, Luke 12:19, 1 Cor. 2:10-16, 12:3) which is of basic importance in the view of man being made in God's image (Gen.1:26). It is stressed that man is a being who belongs not to the earth, but transcends it because he belongs to God (Matt. 10:31, 12:10).

Man has a creative mission in regard to nature, and in transforming human life in the direction of wholeness and fulfilment. We need to create with care and love. God said when he had made the universe, "behold it was good" (Gen. 1:12,18,21,24,31), however as from His commands to us, nature is not static, but we need to have a dynamic view. We should, however, remember the distinction between the creation of the world, as in Gen. 1:1, where the word "bara" is used as "creating", is different to the word used, "asah", for the "making" of the things in the world, which finished with a Sabbath rest (Gen. 1:2-2:2), a rest that we may forget to take. The land was to be used, with a period of sabbath rest for nature (Ex. 23:10-11; Lev. 25:1-7) as well as for man. The divine making of the 'works' of creation finds its analogy in the work of human beings (Ex. 20:11, 31:17) (Moltmann 1985). However, the purpose of God putting man in the garden of Eden was to cultivate and guard it (Gen. 1:25). Not all the plants could be eaten. Man was not put there just to enjoy it, but to till it and keep it. Man has a responsibility to keep the garden. Man is to care for the land (Lev. 25:1-5), to treat domesticated animals properly (Deut. 25:4) and to respect wild life (Deut. 22:6). We can only take what we need. We are nature's keeper as well as our brother's keeper. God will

punish those who bring ruin to nature and the earth (Is. 24:5-6, 45:18, Rev. 11:18). There is an amazing mixture of life (Psalm 104:24,25, Rom. 1:20) all is intertwined, in a delicate ecosystem, which should not be disrupted. We could use the image of participation in the community of nature rather than domination of nature (Moltmann 1985). In the laws of Israel one of man's duties was to respect life and submit to the order of creation (Ex.23:19, Deut.22:9). The created order was made for its own sake, not simply for man's needs and interests (Job.38:2-4; Ps. 8:3,4, 19:1-6, 65:9-13, 104, 136:4-9, 148; Jer. 8:7). However, often the earth has been viewed as merely the material stage on which the drama of human history has been played out on. Mastery over nature should not be explored in a loveless attitude, in a spirit of exploitation, but with reverence for all creation, as a gift entrusted to our care. It is true that all of creation groans together and is in pain together under the influence of man (Rom.8:22). Although a cocreator, coexplorer and coworker with God, man is under God's authority, and should be obedient (Phil.2:5-11). Man can become part of God's creation, consciously, cooperatively, creatively and intelligently acting in the ongoing process of creation. Creativity is part of the potentiality God has given to us (Peacocke 1986). It could be significant that the moral test comes in terms of man's relationship with nature.

The theocentric approach challenges two common tendencies. Eastern religions tend to blur the distinction between God, man and nature, leading to a glorification of nature. However, Judeo-Christian belief is in a divine God who made the world (Gen. 1-3), the world itself is not divine. Western, or industrialised thought, tends to divide man from nature, seeing nature as something to exploit for man's comfort. We must remember man is a creature, part of nature (Psalm 103:15-16), and that pride is a sin (both pride of species and our achievements). We are currently in a crisis of domination, not just an ecological crisis, but a crisis of our whole life system, brought upon all of creation by ourselves. The origin of this crisis is in human behaviour and attitudes, and the tremendous power of our technologies to shape the world. As a reaction against this some people attack what they see as the cause, science and technology, and its effect upon people's philosophy; however, the real cause is the age old problem of human sin and selfishness, which is now days exemplified in the short term economic desires of many businesses and governments. As we begin to understand the consequences of our actions upon the world, and the often far-reaching consequences of them, such as the dramatic effects of the changes we have made on the earth's atmosphere (destruction of ozone, production of carbon dioxide, or acid rain), the extinction of many species, and the tolerated starvation of many people.

There have been some who argue for a reverence for all life, such as Albert Schweitzer (1966). This approach makes no distinction between higher and lower life forms, saying that a Christian can not judge other lifeforms in relation to ourselves. It does make the point that it is very difficult for us to understand or judge the importance of other living organisms in the natural order. Even if animals an look to be meaningless, they have a distinct purpose. In fact the Bible does teach a respect for all of creation, it all has value, but other Christians would say that the Bible gives examples of our use of animals as is not surprising in the agricultural society that the Bible was written in. Schweitzer made reverence for life a fundamental principle of life. He said that the killing of animals in contrast to the harvesting of plants and fruit, is very similar to homicide. The only reason for

harming life he sees is for necessity. However, what is "necessary" can vary widely between cultures, and the Bible indicates that man does not survive on the minimum possible, their is time for feast and for fasting, seen in the lives of Jesus and the disciples. It is not possible for a Christian to insist on vegetarianism, from numerous scriptural references, but animals should be used with restraint and treated humanely, including their killing. The motive behind the use of animals alters the morality of their use in some religions and in some philosophical systems.

Having considered what people may think of when they think of nature, and what the dominant religious views on nature and the role of humanity is, we can consider objections that are expressed relative to this theme.

Playing God

In Judeo-Christian traditions the term "Playing God" is a term applied to situations where humans make life or death decisions without reference to God and perhaps even the opinions of other people, this being seen as pride or arrogance. It is not the use of power and creativity that is wrong, but rather attributing power to our own resources (Boone 1989). What is wrong is not the act itself, but the attitudes that could be involved. However, useful applications of technology are positively advocated in Judeo-Christian tradition as part of good stewardship of the earth's resources.

There have been many accusations that scientists are "creating new life forms", however, our present technology is capable only of transferring one or two genes into a genetic background containing the order of a hundred thousand genes. In the case of chimeras, rather than a new life form being created, two species may be combined that were closely related, for example goat and sheep. However, this type of experiment is not in widespread use and is not expected to be used except for a few scientific experiments.

The expression usefully suggests that we should be cautious in the use of technology whose potential risks and side-effects we do not fully understand. The idea is that while God may understand all, we do not, so we should only tamper cautiously with things as basic as genes. The question is whether we have the necessary knowledge and wisdom to successfully alter lifeforms that have come to us after a long period of adaptation, without creating long-term and catastrophic eco-disasters. This is one of the major reasons that long periods of restricted laboratory, and controlled field trials are required prior to any introduction of GMOs into the wider environment. It reflects the unknown ecological "safety" of the new variety, and risks of gene transfer. It is a question which requires practical knowledge from controlled experiments to assess, and will be discussed in chapter 8. We should use new technology if it is better than old technology, but there will be situations where we do not use it because of unknown or unethical applications.

For some there is a feeling that we should not explore all the secrets of life, that the mystery of life will be gone if we discover too much. However, as many scientists will say, the more we know, the more appreciative of the workings of life we become. Discovery itself may not be wrong, but how we use it or abuse it raises ethical questions. The fact that we have practical requirements, such as to feed, house and heal people of the world, are major justifications for the pursuit of practical knowledge in any system of religion or philosophy that places a high value on human life.

Interfering With Nature

There is also a "non-interventionalist" idea among some, that we should not interfere with nature as "Nature knows best". However, we just need to think of the many diseases that afflict humans or other living organisms, to falsify this idea. There is a clear mandate for some degree of interference with nature even in human existence, as we must eat, let alone use the many medical techniques developed. At the same time people have at last become more aware of the damage to the environment and to other species that human intervention has caused, such as the greenhouse effect, depletion of the ozone layer, or the extinction of many species.

The objection lies more in the idea that genes are a foundation of life. The idea is that genes in some way are more sacred than other parts of the organism. However, DNA and entire genes can be made by purely synthetic procedures in a laboratory. There is also the idea that altering genes is a novel idea. A new catch phrase is "Genethics", which may highlight some concerns (Suzuki & Knudtson 1989). They suggest that the problems raised by genetic technology cannot be dealt with ethically by existing ethical principles, or by Western morals, and we must turn to Eastern religion. This conclusion is not shared by this writer (Macer 1990a). In the Western tradition, there are two balanced principles which summarise the approach needed. We need stewardship of the earth, and we support the creativity of man to find new technology and to use it in a way that is consistent with proper stewardship. Unfortunately, we often forget or were ignorant of bad environmental consequences of our technology, but now that we know more, we should be regrasping the meaning of stewardship. While the use of genes may be seen as novel, we have had a very long history of genetic manipulation using conventional techniques of plant and animal breeding, but only recently do we understand the details of why they worked. We should consider our knowledge when implementing any new variety of organism, however it was made.

The negative science fiction image has been easily promoted and is appealing to the human imagination. The fascination with creating "new forms of life" is coupled to a fear of how far it might be taken. The Frankenstein Factor was coined by Gaylin (1976) as a suitable name for the wild scenarios imagined by some people, which represent the fear of the unknown, as symbolised in the movie. There are many movies which play on similar themes, and this has been very powerful in shaping public perceptions (Rollins 1986).

Integrity of Species

Modern biologists generally think of species as reproductive communities or populations. The species are limited by an arbitrary limit to variation. There is no universal or absolute rule that all species are discretely bounded in any generally consistent manner (OTA 1989). One species may exchange little or no genetic material with related or adjacent species, while another may seem to be almost promiscuous, inbreeding frequently with a neighbouring, related species. To challenge the integrity of a species requires more than a single gene change. Mammals like mice contain 50,000 or more genes and changing a small number of genes will not violate species integrity. Species exist in nature as reproductive communities, not as separate creatures.

Both cell fusion and recombinant DNA techniques allow species barriers to be readily overcome. Cell fusion can be used when the characteristics of interest are controlled in a complex manner by a large number of genes, so that large portions of the genome can be combined. This technique is used on a large scale in the commercial production of monoclonal antibodies.

People are more concerned about the manipulation of animals than of plants and microorganisms, because they are sentient beings. Preservation of each species as a species is important, so we should not lose each species' identity, but the question of changing genetic identity is harder to answer. Genetic engineering does breach natural barriers between two classes of living things. The new strains should not be thought of as special, manmade, forms of life, considering the wide genetic variation naturally occurring. The experience of the last fifteen years work with recombinant DNA involving mixing genes from different species, has not indicated any inherent danger in the source of DNA, whether it be animal, vegetable or human. Any possible danger comes from the type of gene, not its source, whether it is a bacterial toxin or an activated oncogene. Adequate laboratory safeguards have been developed for contained experiments.

People may voice concern about their fear of the destruction of wild species if we introduce transgenic varieties. However, transgenic strains made with controlled gene integration may be considered within the naturally occurring range of variation, and most of the animals of exceptional variety are confined to laboratories. Organisms used for agricultural production are traditionally kept separate to the wild species, and this will continue with new varieties. Modern breeders should realise the need to maintain stocks of the original species and the importance of maintaining wide variety of wild species, in seed or germ plasm banks. If this precaution is taken, than there is no danger of losing old varieties as has happened in the past for some organisms.

A technique for genetic manipulation of animals involves embryo manipulation using cells as carriers of the novel genetic information. Animals can be grown from chimeric embryos, that is embryos that are made by mixing cells derived from genetically-different sources. A chimera can occur naturally, they can develop normally even if their cells are of two different genotypes. They do not have any problem of immune rejection of one set of cells, as the development of the immune system and what it sees as itself, takes place during the development of the chimeric animal. It will recognise all cell types as itself. These chimeras can also be made from multiple different cell types.

One of the most publicised outcomes of embryo splitting was the creation of the sheep and goat hybrid, in this case an interspecies chimera. One of the aims of these experiments was the study of development and the immunological relationship between the female and the embryo. The embryonic cells used are blastomeres and may be from different species, like sheep and goat, which were used to make the so-called "geeps" (Fehily et al. 1985). The hybrid chimeric embryo from mixing sheep and goat embryonic cells developed into "healthy" hybrid adults, displaying a mixed physiology and behaviour. It is also reported that sheep and cow chimeras have been attempted. The skills of manipulation are growing, and this is another cause of concern. Some hybrids will not develop as they are rejected by the mother, but this may be overcome by only substituting the cells into the inner cell mass, leaving the trophectodermic shell around the outside of the embryo, which develops into the

placenta, to protect the new embryo. This has led to sheep being able to give birth to goats, and vice versa. This type of embryo transfer technology may also be important in attempts to preserve some rare species, by using domestic animals as surrogate mothers. These chimeras are used for the study of cell differentiation and interaction in the developing and mature organisms.

The greatest public concern is over the mixing of human and animal genes. People object to the insertion of human growth hormone genes in pigs. Since much transgenic animal research is aimed at increased understanding of human diseases, the insertion of human genes will be very common. Other research also involves the insertion of human genes into animals. The reason for this is convenience, as a large number of human genes have been cloned. The most convenient, readily available form of a gene will be used for manipulation. It is unlikely that animal genes will be introduced into humans as therapy at this stage, and it is unlikely that any will be needed as the appropriate human genes should be available.

The popular press sometimes reports claimed human/animal hybrids. One claim made by an anthropologist at the University of Florence, was that anthropoid embryos, using the sperm of a man and the egg from a chimpanzee, had been made in laboratories. The wording was such, that after the embryo was established, the experiment was terminated, implying that it may have continued (Schmetzer 1987). Human and animal gametes are often mixed in fertility tests performed at *in vitro* fertilisation (IVF) research centres. It is unlikely that a functional preembryo could be formed, though the egg may be triggered as if fertilised. Even if a zygote was formed it would naturally die as the genomes are dissimilar and the preembryo would cease to divide. IVF may be considered by the public to be one of the techniques of genetic engineering, but it is not considered as such by scientists. IVF is required for certain types of genetic engineering. The most likely work that could produce a human/animal chimera is using mixing of embryonic cells, as for the geep, but this work is prohibited in many countries.

Reducing Genetic Diversity

Most of nature could survive without much human intervention, but as natural areas become modified by human activities, there will need to be increasing dependence on the intervention of specific technologies to maintain the diversity. Biological diversity refers to the variety among living organisms and their ecological interactions. There are three layers. There is ecosystem diversity, where there is a landscape interspersed with croplands, grasslands and woodlands. There is species diversity inside of each of these areas, which can be reduced by grazing for instance. There is genetic diversity, many wild plants have greater diversity than crop plants which have be bred for specific characters (OTA 1989).

There are several concerns for this problem. The first two are anthropocentric. The loss of plant, animal and microbial resources may impair future options to develop important new products and processes in industry, medicine and agriculture. The loss of diversity undermines the potential of populations and species to respond or adapt to changing environmental conditions. Because humans ultimately depend on the environment it is essential not to disrupt the environment. There are also aesthetic and ethical motives to avoid the irreversible loss of unique

lifeforms which plays an increasing role in conservation issues. We are told that some of the plants were made to look beautiful (Gen. 2:9), and there are many writings illustrating the beauty of nature (Ps. 19:1-6, 104). Certain areas or species have major significance to some cultures, and nations, such as the bald eagle for Americans or the Kiwi for New Zealanders. There is also an economic reason to add, which is favourable, that of tourism, which may help some situations and disturb others. For example in Kenya, in 1985 the income of US$300 million made wildlife tourism the country's biggest earner of foreign exchange (OTA 1987a).

Because the abundance and complexity of ecosystem; has not been able to be assessed, an accurate estimate of the rate of loss is not currently possible. This is especially true in the tropics. While only 1.7 million species have been identified, 5-10 million remain yet to be identified. Recent research in the canopy layers of tropical forest found so many different insect species, that the number of total species is probably closer to 30 million. Thousands of species are being lost, especially in the tropics. The problem of diversity loss is broader than the extinction of species, because diversity losses can occur at each level of biological organisation. Ecologists categorise the types of ecosystem. For instance in the United States 23 types of ecosystem covered 50% of the area when Europeans settled, but now they only cover 7% of the area. The agricultural states have had the highest loss of natural ecosystems, around 90% in Iowa or Illinois. Within these ecosystems, species diversity is much greater in the tropics, for example a single tree in the Peruvian Amazonian Rain forest was found to harbour 43 species of ant belonging to 26 genera; this species richness is about equal to the ant fauna of the entire United Kingdom. The current rate of loss of species is greater than the estimated rate that species evolve.

Reduced diversity has major consequences. It eliminates the options to use untapped resources. For instance, the use of wild crops in breeding crop plants has accounted for half the production increases, and is estimated to account for US$1 billion annually in U.S. Agriculture. Future gains will also depend on the use of genetic diversity as well as genetic manipulation. Nature provides the raw materials, the genes. There are also direct benefits of wild species such as the role in pollination, where the pollinators need alternative breeding sites, and food sources when the crop is not flowering. The affects can be through several species, for instance the Californian wild brambles provide an off-season reservoir for the prey for wasps, which are important for controlling a major grape pest. The economic benefit is about US$60 an acre in direct pesticide cost savings, plus the indirect benefit of reducing pesticide use. About 25% of the prescription drugs in the U.S. are derived from plants, with a market value of US$8 billion annually. Many potential drugs remain to be found. There are also many diverse species specifically used for scientific research because of their perculiarities. The oldest living organism is Bristlecone pines, which are very important for the calibration of radiocarbon dating, used in archaeology, prehistory and climatology. Many species are important for biological research because of their special properties, such as tolerance to environmental conditions like the desert pupfishes of South West USA which live in twice the salinity of sea water and are used in study of human kidney disease; or animals that suffer from human diseases such as the Armadillo which can suffer from leprosy; others have enzymes which can be used in bioassays, such as extracts from horseshoe crabs used to test vaccines for contamination with bacterial

endotoxins; or the antibacterial products such as penicillin and other antibiotics from fungi, or antiviral agents like D-arabinosyl cytosine from a Jamaican sponge. These examples just illustrate how great the variety of useful organisms there are in nature.

On the higher level are the environmental regulatory factors which depend on complex interactions of ecosystems. For example wetlands are very important for the breeding of birds and fish, crustaceans and molluscs. They also temporarily store flood waters, which is a direct benefit. The Charles River wetland in Massachussetts are estimated to save US$17 million a year in flood control. Often we overlook the value of ecosystems. As we can now understand, if we alter nature on a global scale, we have proportionately larger problems, as seen in the greenhouse effect. There are several contributory factors, one is the doubling of the carbon dioxide concentration in the atmosphere in the last century by burning of carbon fuels and forests, and the reduction of forested area. The temperature of the earth rises, which alters the sea level, the climate, the vegetation and hence the animals in particular areas. There are also other gasses released which contribute. We also have the depletion of the ozone layer by chlorofluorocarbons which has resulted in greater numbers of human skin cancers appearing.

One of the oldest ways of destroying nature has been the use of fire, for driving game in hunting, or for clearing land for agriculture. It is the cause of many of the world's present grassland areas, and also deserts. Added to this destruction of forest was the use of wood for building homes, etc. Environmental problems may be able to be traced back to the beginning of civilisation, but are getting worse with the global scale of air and water pollution, the introduction of new chemicals, and the large human population which had led to more overgrazing. Many losses are unintended and unforseen, such as the acidification of lakes in Scandinavia and Canada from the acid rain from the burning of carbon fuels.

Uniform crop varieties are economically useful. Having a field of wheat that grows to the same height, producing good heads of grain which can be harvested at the same time, which is resistant to all known pests and diseases, and has uniform milling properties, is an ideal. Improved crop varieties have increased food production, but have contributed to genetic erosion. Old varieties of crops were dropped in favour of new uniform ones, over a short time period in developing countries, and a long period in Europe. This means that the genetic variability that has been relied on for plant breeding is being lost (Sattaur 1989). There have been several dramatic examples of crop failures due to a lack of diversity. The nineteenth century Irish potato blight caused many deaths. In 1970, the USA lost half its maize crop to one disease, the southern corn leaf blight. The wheat variety Bezostaja was grown in the USSR, over an increasing geographic range in a period of mild weather, but in 1972 a harsh winter led to huge failures in production.

There has been rejection of the claim that new crops will further reduce biological diversity. In some countries, such as Holland which is very densely farmed, farmers may be paid to leave their fields fallow. This is because of the improved productivity of the land. The land can be released for other purposes, such as reverting to the wild. This means other species can reestablish themselves, such as wildflowers. Within twenty or thirty years the amount of land release in Europe as a result of increased agricultural productivity from biotechnological advances may be close to half. Of course the picture is not so good in countries with high birth rates, who will need to expand food production for some time yet.

The environment should be protected by using these techniques.

There is the objection that cloning would reduce the genetic diversity of a species. This would only apply if we were making a significant proportion of the breeding population asexually. We should always try to maintain diverse organisms, as they tend to be better able, as a population, to survive major diseases or environmental changes (OTA 1987a). New genetic techniques are being used to save the remaining genetic diversity, and will enable the practical use of many widely dispersed genes. The involvement can be at many different levels. DNA Fingerprinting has been used to study the genetic diversity of different species. Populations of black rhinos in Kenya, Zimbabwe and South Africa have been found by this technique to be genetically similar, these scattered animals can be gathered together and encouraged to breed. The black rhino is endangered by poaching, so pooling rhinos into protected areas may protect them, and this has been shown to be genetically feasible by the DNA Fingerprinting.

Embryo manipulation is being used to help protect some of the endangered species against extinction. We are losing many species every year, and will lose even more in the next few decades with the major climatic changes caused by global warming. As plants die and move, the animals dependent upon them also may die if they can not change or have nothing to eat. The plants can be modified to survive in the different climate, and some American researchers are pursuing this approach in attempts to save endangered bird species together with the forest communities.

There are major international efforts to save existing genetic variety through germ plasm storage. The techniques of biotechnology should aid the safe storage and regeneration of such germplasm. Genetic engineering itself may have a minor role in the pursuit of this goal. It should be possible to use the techniques developed in chimeric embryo manipulation to allow a common species to gestate the embryo of a rarer species.

Slippery Slopes

The idea here is that because we perform some action, we will perform another. It implies that since we have done something we will not be able to refrain from doing something else. This expression envisages a muddy slope where footing once lost cannot be regained, and suggests that controls which are adequate for initial exploration may fail under increased pressure. The argument is that if we alter the genes of plants and animals, then we will proceed down the slippery slope with human genetic engineering. However, a suitable analogy could be the experimental use of animals. While there have been several examples of human experimentation during the last 50 years, the widespread establishment of ethical committees should preclude any further abuses. There is a moral gulf between support for human eugenic measures and agricultural breeding, which suggests that there is, in fact, a logical place to stop. Feasibility does not mean inevitability. However, we should be sure that our society does stop extrapolation of this kind.

When people talk of genetic engineering they may confuse it with other controversial medical technologies. It may be put in the same category as new reproductive technology, such as IVF and embryo experiments, which are really

very different issues. Opponents may also assert that the final goal of improvement of genetic engineering techniques is "perfection" of the human species. This is not a goal that many share, rather the techniques are pursued for more immediate attempts to find cures for diseases or to improve agricultural production, which are worthy goals in themselves, and more universal as worthy motives.

Cloning is another topic that has long been talked of. There are different types, but the type most talked of is nuclear transplantation from adult cells so that many new clones of an adult can be made. This technique worked with frogs, but there is no prospect of it being used in humans as during development human genes necessary for embryonic growth are irreversibly turned off. There have been earlier claims of the artificial activation of ova of rabbits, but this is not cloning (Pincus 1939). There was reported to be successful nuclear transplantation in mice to produce clones (Illmensee & Hoppe 1981) but this has not been repeated. It is not thought to be possible.

What is quite possible, and currently performed commercially in agriculture is embryo splitting to produce identical twin clones. It is possible for humans too, but is outlawed in Europe. Because it will become widespread in agriculture does not mean that it will be applied to humans.

Many stories appear in the popular media, that are shown to be hypothetical. It has been claimed that it will be possible to recover enough genetic information to bring an extinct species back to life. It is possible to analyze the DNA from ancient species, but it is a very distant prospect to bring about the rebirth of that species. Of course, with the many recent "extinctions" of species whose germ plasm is safely stored it will be possible to bring them back, but they are not really extinct. Embryo transfer technology has been used by the Cincinnati zoo to bred rare antelopes, called bongos, by transferring bongo embryos to eland antelopes. It is also being used at London zoo to attempt to save the wild Indian bison, guar, from extinction by use of a Friesan cow as a surrogate mother. Also in Britain zebra foals have been born to horse mares.

In South Africa, embryo transfer techniques are being tested on wild animals for possible commercial application for game reserves. Embryos of the rare sable antelope are being transfered into surrogate gemsbok antelopes (Armstrong 1990). Wild animals tend to be much more stressed then zoo animals, which makes success more difficult. However, if the technique works there are many important possibilities, such as using white rhinos as surrogate mothers for the endangered black rhinos. Like IVF, embryo transfer is not genetic engineering in scientific terms, but it may be seen as such by the public. This technique is far from being one to generate fear: it may be able to help retain some of the genetic diversity that others are blindly destroying.

Biological Warfare

One unethical use of these techniques that is of grave concern is their major use in the military sphere, although biological weapons are outlawed by a Geneva convention (Dickson 1986). This research is claimed to be defensive (Smith 1984), but there is really no distinction from offensive, as in order to safely commence germ warfare one should be immune to what one is releasing. It is very easy to

engineer toxic bacteria. For example, the genes controlling toxins such as those of cholera or botulinus can be put into the normal human intestine bacteria E.coli. Numerous more lethal combinations have been constructed (GB 1987, Kamely 1989). This research is already here, difficult to stop, but like a nuclear holocaust, their use can be prevented.

Between 1980 and 1987 the real amount of money spend on biological warfare research by the USA quadrupled, and the amount of basic research that is related to this area greatly increased. The USA has built a large maximum containment facility for the testing of such weapons, even though the 1972 Biological Weapons Convention bans the development of them. The research is claimed to be defensive, but as stated above, there is in reality no difference to offensive development. In fact, a vaccination program for the general public would be too expensive, the only effective use for a defensive vaccine would be to give to soldiers who were going to use such weapons.

It is not an argument to stop further new, potentially beneficial research. Military motives do fund much research which can be applied to civil use, but the motivation is wrong. I will not discuss how we fund research, but once the knowledge has arisen from whatever funding, we must still decide how and whether to use it.

People may make claims about the ethical neutrality of science. This implies that scientists do not have responsibility for the production of knowledge. However, this belief confuses the findings of science, which are ethically neutral, with the activity of science, which is not (Bronowski 1965). Some pursue the neutrality argument, by claiming that the moral burden lies with those who choose to implement knowledge for all purposes. We may not be able to predict the abuses of pure knowledge, however, scientists are still moral agents and must think in advance of the possible abuses. They may not be solely responsible, but they share responsibility.

Public Perception of Science

Public Attitudes to Science

The public attitude to science is important, especially considering that most science is publicly funded. The consequences of scientific research will be felt by the public, though these may be impossible to fully predict. In contentious areas such as genetic engineering the issue of public attitudes becomes more important. Adverse opinion, even if that of a minority group can result in protest action as seen in recent examples of the animal rights movement, abortion protests or protests over the release of GMOs. The most sensitive area of science outside of medical issues such as abortion, is the use of animals for experiments. There have recently been terror campaigns conducted against scientists and laboratories involved in vivisection. Scientists have been given a warning that they need to educate the public, and have favourable public opinion with them.

In mid-1989 the public attitudes to science in general were probed in the UK and in Australia . The results of this poll to some key questions are interesting, and fairly favourable, even though the knowledge of science is poor. Asked the question "overall do science and technology do more good than harm, more harm

than good, or about the same of each?", the British public thought 44% more good, and 9% more harm, and the Australian public thought 56% more good and 10% more harm. In Britain 74% agreed that many of the world's problems can be solved by scientific research, in Australia 65% agreed. 76% of the British and 63% of Australians thought that national prosperity depends on science and technology(Kenward 1989). In both countries about 80% of the public thought that politicians do not understand science.

Another survey was conducted in 1988 which showed that the public in the UK and the USA are more interested in science than things like sport, however they show little knowledge of it (Durant et al. 1989). There are biennial surveys conducted for the US National Science Board which have consistently portrayed strongly favourable attitudes towards science. These also suggest the public can distinguish between science and the adverse effects of certain technologies. As with all these surveys, there is greater interest in science and technology among those with more education

In mid 1990 a survey of the attitudes of the New Zealand public to science found that 75% stated that they were interested in science in technology, and 27% said that they frequently watched science and technology programmes on television (Couchman & Fink-Jensen 1990). 79% occasionally or frequently watched television programmes about science and technology, 66% occasionally or frequently read media articles about it, but only 41% read occasionally science and technology magazines. 75% said that they thought science should receive more government funding. These results suggest that the public has a good image of the use of science. Among farmers there was a significantly higher interest in science and technology. This public interest in scientific progress has, and will continue to, aid the expansion of biotechnology and the use of genetic engineering techniques. A US survey in 1986 found that nearly 80% of the public supported the expansion of biotechnology industry in the USA (OTA 1987b), but this feeling is not common to all Western countries. In that survey, 71% of the American public said that they were interested in science and technology, and there was a trend among those without college education to be less interested in science, than a 1982 survey. The US survey considered how frequently people read material on science, but in the New Zealand survey it was found that more people watch science on television than read it in magazines, which is a useful point for future surveys. It is also useful for those who wish to advertise science, television is a better media in terms of reaching the most people, and also a more diverse range of people.

In the US survey, the public were also asked how much risk they thought would come to them or their families from science and technology. 22% thought a lot of risk, and 49% some risk, which is a large proportion of the public. Asked how much benefit they saw coming from science, 41% said a lot, and 39% some. They were then asked if they thought the benefits will outweigh the risks, and 62% thought the benefits would, but 28% thought that they would not. This reveals a key point of science and technology, it is seen to involve both benefits and risks, and this is certainly true. People can entertain thoughts of both benefit and risk from the same technology, and genetic engineering is a good example.

In Germany there is much distrust between scientists and their critics. The factors that have led to this include public dismay over Chernobyl, the Bhopal accident, and other major chemical spills. Many politicians are against biotechnology

and talk of genetic engineering in a negative way, which also creates a bad impression. In 1988 surveys of the Japanese and American public found that only 42% of Americans would support a ban on creating new forms of life, but 67% of the Japanese would support such a ban (Joyce 1988). Even if only 10% of Japanese public say they know what DNA is, 42% thought that the rules covering genetic engineering were too slack.

Public Support for Biotechnology

During the last decade there has been a widespread acceptance of the use of biotechnology and genetic engineering in many countries. The assessment of public opinion is difficult, but opinion polls are the only real way. Face-to-face, non-leading questions with open responses are the best method, but they are also more expensive than telephone polling. Since the eruption of debate in the 1970's public opinion has turned to favour the use of genetic engineering techniques, though with limits of course.

In a 1987 poll of the U.S. public, close to 80% of the public thought that it was good to develop these techniques (OTA 1987b). However, 77% agreed with the statement that the potential danger from GMOs is so great that strict regulations are necessary, though 55% thought that the risks of genetic engineering had been exaggerated. This was despite their lack of knowledge about the techniques involved. Most people agreed with the specific environmental or therapeutic applications that were suggested, but the amount of approval varied with the proposal. Asked, "if there was no direct risk to humans and only remote risks to the environment, would they approve of the environmental use of GMOs with the following characters", the numbers that approved were: disease resistant crops 73%, bacteria to clean oil spills 73%, frost resistant crops 70%, more effective pesticides 56%, larger game fish 53%. Even if the risks of damage to the environment were high many people would approve, for example if the risk was 1 in 1000, 55% would still approve if the product would significantly improve farm production. While the public can respond to such questions, the perception of statistical risk is very difficult, and can only be used to support general statements.

A Japanese Government survey of 3000 adults in the late 1980's, indicated 67% did not know of DNA. An independent survey was conducted by the magazine *Newton* (1989), a popular science magazine with a circulation of 300,000 in Japan. They picked 500 people from their readers at random with a weighting towards people living outside of large cities to get a more unbiased view. The readers of this magazine are all interested in science and technology, it is a selected sample rather than a public survey, but is still useful.

The results showed that the readers have heard of specialised techniques, but could not explain what they were. 98% knew the word "biotechnology", and 70% were interested in it, with most being a little interested. 77% thought biotechnology is rapidly developing. Although they showed good knowledge about DNA or genetic engineering, they think biotechnology is difficult to understand. Only 20% thought biotechnology has an image of being complicated and about 30% thought they could explain how DNA works to other, and about 60% thought they understood. They were asked about different techniques, both if they had heard of them and which they could explain to others. The results are presented in Table 3-1, (%'s of respondents that had heard of, and those who could explain it to a friend).

Table 3-1: Results of Japanese magazine survey of awareness of biotechnology techniques to readers (Newton 1989).

Technique	Have heard (%)	Can explain (%)
Chromosome manipulation	71.3	31.1
Microinjection	27.3	7.7
Cell fusion	61.7	26.3
Cell culture	71.3	33.3
Bioreactor	24.0	9.3
Genetic recombination	98.3	17.3
How does DNA work?	93.0	27.6

Many people understand the fears of the protest movement against genetic engineering, but 30% supported the protesters. I will present more results on the attitudes to novel foodstuffs in chapter 9. They were asked of many more specific examples, which can be a better way to assess real knowledge of a technique. Of the people surveyed, 48% knew that scientists were trying to make a common fish, Ayu, bigger by biotechnology. Only 15% thought this would be good if farmed, but 60% were a little worried, and 16% worried about this. Asked whether they supported the production of herbicide tolerant and insect resistant plants, 34% thought it was good, but 59% were at least a little worried. With spraying genetically engineered microorganisms onto crops, only 15% thought this was good, but 43% were a little worried, and 35% were worried. About 30% agreed with the protesters who said there were risks in releasing GMOs, and another 58% said that they understood the fears of the protesters, and only 2% said there was no danger..

In summary the survey showed that 77% were worried about the dangers of biotechnology, and over half thought they could not trust the researchers. 25% supported protesters who were opposed to P4 and P3 contained laboratories in Tsukuba and Shinjuku, Tokyo. 88% thought that researchers would hide bad results or dangers from the public. This survey was conducted among people of a higher than normal science knowledge, so is worrying.

There was a public opinion poll carried out by the Commission of the European Communities in 1979 which included attitudes to genetic research. The public opinion in different countries ranged widely, with the percentage of those people thinking genetic research was worthwhile being 49% in Italy, to 22% in West Germany and 13% in Denmark. There was a reciprocal relationship with those people who thought genetic research had unacceptable risks. It is not surprising that there has been more recent opposition to biotechnology in Denmark and West Germany (Tait 1988). There is much concern remaining in Europe about field testing of GMOs. There have also been some very active protest movements, which may represent minority public opinion.

In mid 1990 a major survey of the attitudes of New Zealanders to biotechnology was conducted (Couchman & Fink-Jensen 1990). The results of the face-to-face interviews with open answers are interesting and some are shown. In a similar style to the Newton survey in Japan, people were asked of their awareness of different scientific terms and whether they could explain them to a friend. The

Table 3-2: Results of New Zealand Public Attitudes Survey showing awareness of different techniques (Couchman & Fink-Jensen 1990).

Technique	Have heard (%)	Can explain (%)
Biological pest control	82	21
Silicon chips	85	25
Biotechnology	48	9
Fibre optics	57	20
Agricultural pesticides	91	30
In vitro fertilisation	75	31
Superconductors	43	12
Genetic engineering	74	20

results of this question are presented in Table 3-2.

These results show that people are more familiar with the term genetic engineering than they are with biotechnology, and considering that the survey was of the general public, a higher proportion of the New Zealand public have heard of these words than in the American and British surveys. A recent survey in the UK showed that only 38% had heard of biotechnology, compared to 91% for silicon chips (RSGB 1988).

The people who had heard of these techniques were also asked whether they thought these different areas were of benefit to New Zealand, "whether these areas would be worthwhile areas for scientific research in New Zealand". The percentage of people who thought these techniques were worthwhile, and those who thought not (there were also some who did not think they knew) were: biological pest control 86% yes/ 7% no, silicon chips 62% yes/ 21% no, biotechnology 72%yes/ 11% no, fibre optics 66%/ 16% no, agricultural pesticides 85% yes/ 10% no, *In vitro* fertilisation 71% yes/ 19% no, superconductors 58% yes/ 19% no, and genetic engineering 57% yes/ 28% no. In light of the benefits that should be expected from genetic engineering that are presented in this book, this final figure is somewhat worrying. There needs to be more education about what benefits can be expected from these techniques, especially to countries that have agriculturally-based economies like New Zealand. There was significantly less benefits seen arising from genetic engineering among those with less education. For those who are interested in further details, this survey is highly recommended.

Those people who responded that they had heard of these techniques were asked how worried they were about the impacts of these techniques. They were asked whether they were not worried at all, slightly worried, somewhat worried, very worried or extremely worried about these techniques. The sum of people who were at least slightly worried about these techniques were: biological pest control 49%, silicon chips 14%, biotechnology 30%, fibre optics 9%, agricultural pesticides 60%, In vitro fertilisation 38%, superconductors 8%, and genetic engineering 55%. It is clear that there is much greater concern about genetic engineering than techniques such as silicon chips or superconductors, however there is also a high level of concern about biological pest control, and pesticides. The level of concern was somewhat higher among those with more education, so that while further education is required, it should not be assumed that people are worried

because they do not know enough. Among those with an undergraduate degree 73% expressed concerns, and 80% of those with a postgraduate degree expressed concerns. 70% of those who could explain genetic engineering to a friend expressed concern, compared with 51% of those who had only heard of the term.

A telephone survey conducted among farmers, and postal surveys among scientists and science teachers shed more light on this subject. The awareness of each area of science and technology was higher among these groups, and they had greater interest in science than the public (Couchman & Fink-Jensen 1990). Farmers had fewer concerns about the use of these techniques, and saw more benefits from genetic manipulation, and had less concern about consuming foodstuffs made using GMOs than the general public. However, their concerns about genetic manipulation in different organisms were not very different to the public at large.

Another particularly interesting result from this survey is the perception of different subjects of genetic engineering, and public concerns. The awareness of genetic manipulation in different areas was asked. Those who were aware and said they thought the research was unacceptable were asked what concerns they had; and those who saw benefits were asked what the benefits would be. Careful care was taken not to prompt the respondents by suggesting any concerns or benefits. These answers make interesting reading (Couchman & Fink-Jensen 1990), but for the purposes of presentation were assigned to different general categories. These are presented in Table 3-3. The concerns are of the type that are expected from international work, and have been discussed in this chapter. As discussed, the unnaturalness argument is very weak philosophically, though it may still remain important. The fear of the unknown is a valid concern, which must be addressed by scientific trials. The fear of unknown consequences for society, can not be so easily addressed, as discussed in this book.

Genetic engineering was seen to be a more worthwhile area of research for New Zealand by scientists, farmers and science teachers than the general public. This may be because the benefits more directly affect these groups, as well as their greater knowledge of the potential benefits. However, scientists also expressed more concerns about genetic manipulation, for the same reason. The reasons for concerns included a greater weight on the ethics of such techniques, and the lack of controls on experiments, or the misuse of knowledge. This was a different emphasis to the public. The fear of the unknown was still common, as were concerns about interfering with nature. Given the nature of these results, it suggests that the topics discussed in this chapter, and those following are topical for those of any position.

Table 3-3: Attitudes of New Zealanders to genetic manipulation in different organisms, from sample of 2034 adults (Couchman & Fink-Jensen 1990). Responses expressed as %. See text for details, those who were **aware** of the techniques were asked whether they thought research was acceptable or not (if not why not), and saw any benefits (if so what?).

Question	Manipulation of genetic material in (%)			
Awareness of?	HUMANS	MICROBES	PLANTS	ANIMALS
Not heard of	35.2	59.0	29.7	31.2
Heard only	39.8	29.4	43.9	43.3
Could explain	25.0	11.6	26.4	25.5
Which,if any,of these areas are unacceptable for any reason?				
Acceptable	42.5	71.1	85.4	56.4
Unacceptable	57.5	28.9	14.6	43.6
Why Unacceptable?	% who included as reasons:			
Interfering with Nature	28	22	35	22
Morally wrong	16	0	0	35
Disastrous Result	16	12	12	9
Unknown area	8	16	11	8
Control Difficult	7	10	8	7
Open to misuse	9	13	8	6
Which,if any,of these could produce benefits for New Zealand?				
No benefits	51.6	37.3	12.5	33.6
Benefits	48.4	62.7	87.5	66.4
What benefits?	% who included as reasons:			
Cure disease	22	14	0	16(animal)
Benefit medicine	29	13	2	3
Improve life quality	22	9	3	6
Advance Science	7	10	0	6
Improve Organism	-	11	38	38
Increase Yields	0	5	23	16

In the American OTA survey (OTA 1987b), there were more questions considering human genetic manipulation. The question that people were asked concerning human genetic manipulation was pointed, in the sense that it asked people whether they thought it was morally wrong or not. 42% said it was morally wrong, and 52% thought it was not. Given more specific applications, they were more supportive, such as to stop children from inheriting a usually fatal disease 51% approved, and 33% somewhat approved, while only 15% disapproved. If the application was to improve the intelligence of children, 39% strongly approved, and 38% somewhat approved; but if it was to improve physical characteristics only 18% strongly approved and 26% somewhat approved. In the New Zealand survey the question about genetic manipulation was contrasted with different organisms. The open natured question allows more analysis of people's reasoning for support or

Table 3-4: Acceptability of different areas of genetic manipulation by different groups of the New Zealand public. The survey of the general public was face-to-face, the rest, biology teachers, farmers and scientists were mail questionnaires (Couchman & Fink-Jensen 1990). The number of respondents in each sample is given, only those who had heard of each type of manipulation were asked for a response.

Genetic Manipulation in:	Occupation of Respondents			
	Public	Teachers	Farmers	Scientists
Human cells				
Heard of (No.)	1318	189	127	171
Acceptable	42.5	48.7	32.3	53.8
Unacceptable	57.5	51.3	67.7	46.2
Microbes				
Heard of (No.)	834	266	82	210
Acceptable	71.7	72.2	64.6	75.2
Unacceptable	28.9	27.8	35.4	24.8
Plants				
Heard of (No.)	1429	266	157	226
Acceptable	85.4	87.3	87.3	82.7
Unacceptable	14.6	12.7	12.7	17.3
Animals				
Heard of (No.)	1400	244	150	217
Acceptable	56.4	81.6	65.3	77.4
Unacceptable	43.6	18.4	34.7	22.6

reservations. There was greater concern among older people about human cell genetic manipulation, which one could speculate might have something to do with the eugenic abuses in the past. Among farmers there was more rejection of genetic manipulation in human cells, but more acceptance of genetic manipulation in plants and animals. This suggests that the farmers had a greater perception of the differences between humans and other organisms with respect to these techniques. However, scientists were more approving of genetic engineering in humans. The comparative results are presented in Table 3-4. The results of both surveys do suggest a mixed opinion over the use of human genetic engineering, especially if for medical reasons. There needs to be education about the implications of such work, and greater discussion about it before accepting that people support such applications.

The world-wide opinion of scientists, philosophers and legislators has turned to be supportive of many applications. The moral premises that may have been behind this are various (Callahan 1979). There is the principle of individual liberty, that we may seek what we desire if it does not harm others. The principle of risk-benefit analysis, that in matters of uncertainty, risks and benefits are to be compared and moral action determined by the outcome of the equation. This has led to the

relaxing of guidelines regarding recombinant DNA experiments. Another principle is that it is better to attempt to do good than to try to avoid harm. A failure to pursue good can even be taken as a form of doing harm, the sin of omission. However, these principles need to be balanced by more examination of what society wants. Although the more highly educated express more concerns, they also see more benefits in the use of genetic engineering.

Public Participation in Decision Making

Public concern is whether the decisions on the use of genetic engineering, which will involve the creation of altered or new lifeforms, will be left to the discretion of individual scientists and corporations. Regulatory and advisory committees will need to have public groups included so that they are seen to be neutral and balanced. Discussion over planned experiments should be in public, which will also aid the education of the public, if done in a reasonable way.

The committees need to have lay members to ensure public participation. This applies to all types of bioethics committees. The lay people should include some people that have relevant experience however, whether it is as a farmer in the case of releasing GMOs, or as someone who has experienced genetic disease in their family in the case of medical genetics committees. A reasonable representation of the society in terms of race and religion should be present, though also including minorities.

Fundamentally, the public must also decide which applications will be supported, and the extent of commercialisation of the technology. It is ironic that much public opposition has focused on the question of the ecological safety of introducing GMOs in field trials. Little attention has been focused upon the long-term goals and consequences of the use of biotechnology and genetic engineering. Certain groups have tried to focus some attention on this, such as the well known activist in the USA, Jeremy Rifkin (Rifkin 1983, 1985, Kimbrell & Rifkin 1987), and some third world conferences (Bogeve 1987). As they state, the first duty of government is to determine the long range consequences of the application of a major technology, and the public should have a major input into this, because there will be major effects upon society. The commercialisation of biotechnology is discussed in chapter 10, together with some of the consequences. We should not just accept that technology will progress and we must adjust society to it (Withers & Kenworthy 1987), but we need to examine the whole foundations of technology and adjust it to the direction society should take. The long-term environmental impacts are also more important than the short term effects of small scale field trials of GMOs.

Education

Scientists in academia and industry fear that unless they explain in full the risks and benefits of genetic engineering, then opposing groups will win the moral high ground and slow down the technology. Biotechnologists must put their views across in an honest and balanced way so they become trusted. Scientists have been living in an ivory-tower and have missed many opportunities to tell the public what is going on. Several campaigns have been mounted which may be aiding public understanding, such as those by the Dutch Government, and by the company

Monsanto who are providing educational materials for distribution. Not only is information given, but public discussion encouraged.

Even the existence of good science journalism and public television science programs can do little to dispel the public impressions created by a single popular movie or editorial cartoon (Zimmerman 1984). The 1987 OTA survey in the USA found that the general public are more inclined to believe environmental groups than federal agencies or companies (OTA 1987b). This trend was also found in New Zealand (Couchman & Fink-Jensen 1990). The suspicion of researchers was particularly evident in the Japanese survey also (Newton 1989). Communicating science to the public is a major problem, as is understanding public concerns. Rather than people being easily divided into pro- and anti- factions, often people may express different thoughts at the same time (Evered & O'Connor 1987).

Government Commissions on Genetic Engineering

There have been government commissions in several countries who examined the questions raised by genetic engineering. The President's Commission in the USA indirectly looked at the issues raised by the new technology when applied to human beings. Unfortunately it was dismantled by a change of government in 1983. There have been other studies in the USA performed by the Office of Technology Assessment on specific issues. These studies continue to provide useful background information, but can not be expected to provide very extensive ethical analysis of particular problems because they usually consider many facets of a technology.

In 1984 a special parliamentary commission in Germany, the Commission of Inquiry on the Opportunities and Risks of Genetic Technology, started looking at these issues, and it produced a report at the end of 1986 (GB 1987, Catenhusen 1989). It produced the most comprehensive single report on the wide range of issues associated with agricultural and medical uses of genetic engineering produced by government bodies so far. The commission proposed some restrictions that they thought should be legally imposed. They recommended that germline human gene therapy should be banned. Military research involving genetic engineering should also be banned. They also proposed a 5 year moratorium on field trials of some GMOs. A total of 170 recommendations were made to parliament, representing the range of topics covered. It has stimulated public debate on the issues, and has provided much information for the politicians as well. Only with good information can informed decisions be made.

There must be further reports made to raise public awareness, so that people can decide. The Swedish government has commissioned a report on genetic engineering, to be completed in 1992. There have been several Government reports prepared in Britain and Australia which covered issues such as IVF, gene therapy or field release of GMOs. Some countries have established bioethics committees to continually examine the broad range of issues, and/or to consider particular projects. This type of standing committee should be encouraged, in addition to a repository of publically accessible information.

4. Medical Ethics, History & Culture

Standards governing the practice of medicine have arisen as a result of continual interactions at the level of the perception and propagation of world views by groups in society intending to maintain or establish social order and the interactions between individuals physicians and their clients. We need to view the historical standards in the context of the people of those times. Conversely, our society is different today, and we may find different standards more compatible with living at the end of the twentieth century.

We can define "morals" as judgements on individual activity, "values" as stated expressions of the cultural framework within which these judgements are made, and "ethics" as socially derived generalizations induced from individual morality. The healing situation requires special morals as it involves a sick, vulnerable person with a healer who is required to help, and not to exploit the vulnerability of the patient. One method of controlling behaviour was the following of ethical codes and the taking of Oaths. There are various ancient oaths that have been discovered (Konold 1978), from various cultures, but the most universally honoured is the Oath of Hippocrates.

The Hippocratic Oath was probably written around the 4th century BC by Pythagoreans, yet it has influenced world-wide medical ethics. It is still taken by over 90% of American medical students (Friedlander 1982). It is the focal piece of a long tradition, what we can call the Hippocratic tradition. There are many important questions regarding why it was accepted and is still so widely used and whether it still has a useful place as an oath, or as a source of principles for medical ethics today.

The Hippocratic Tradition

Medicine had been practised in the Near East and Egypt, Assyria, Babylonia, Persia before the rise of Greek culture. There was a flow of ideas between these trading states in the period three millenium ago. In the fifth century BC medicine in Babylonia and Egypt was practiced subject to strict state control (Aristotle I). There had been previous attempts to protect patients from incompetent doctors, the first recorded one being the Code of Hammurabi in 1727B.C. The Code stated the respective damages to a doctor for negligence when operating on Nobleman or Slave (Carrick 1985). There was also a regulation for the setting of medical fees based on the socioeconomic status of the patient (Nos. 215-217, Nos. 221-223). There are no surviving records of characteristics of the ideal physician from Assyro-Babylonian and Egyptian cultures, but there is a Persian description from the sixth century in the Sassanian Persians *Dinkard* (Amundsen 1978a). However, the physician refered to was a magician in this culture, involving supernatural elements. There does not appear to have been any prohibition on euthanasia (Carrick 1985). There were laws

against abortion though, in the Persian *Vendidad*, and as early as the fifteenth century BC in Assyria (Amundsen 1978a), however there are prescriptions for abortive drugs in Egyptian medical papyri. It is not clear what the opinion of practising physicians in these cultures was before the rise of Greek medicine, and it is unlikely they had much influence on Hippocratic ethics.

The standard english translation of the Hippocratic Oath (Edelstein 1943) is:

I swear by Apollo Physician and Asclepius and Hygieia and Panaceia and all the gods and goddesses, making them my witnesses, that I will fulfil according to my ability and judgment this oath and this covenant:
To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art - if they desire to learn it - without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken an oath according to the medical law, but to no one else.
I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.
I will neither give a deadly drug to anybody if asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art.
I will not use the knife, not even on sufferers from stone, but will withdraw in favour of such men as are engaged in this work.
Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slaves.
What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of men, which on no account one must spread abroad, I will keep to myself holding such things shameful to be spoken about.
If I fulfil this oath and do not violate it, may it be granted to me to enjoy life and art, being honoured with fame among all men for all time to come; if I transgress it and swear falsely, may the opposite of all this be my lot.

The author of the oath is unknown, but it is generally assigned to Pythagoreans after the detailed critique of Edelstein (1943). The Pythagoreans were one of the first groups of philosophers to take a serious interest in medicine. Some of the passages found in the Hippocratic Oath are incompatible with other works of the Hippocratic Corpus, and some of the ethical advice is clearly different to the practises of many Greek physicians. Different authors and groups wrote various sections of what was gathered by later physicians as the Hippocratic corpus.

The medical tradition is commonly called the Hippocratic Tradition, so prior to considering the Use of the Hippocratic Oath and the associated tradition, it is necessary to define the actual "duties" on the Oath-swearer. Some of the ideas today associated with the Hippocratic Oath are not to be found in the Oath itself. It is used as a basis for many traditions, from the quality of medical education, the idea of confidentiality, the importance of the person, the idea that medicine is more than a science but an Art of comforting (Guthrie 1957), the advancement of the profession rather than the individual doctor (MacG-Jackson & Short 1966), and the idea of medical consultation for the benefit of patients.

A Profession

The first part of the oath is like a covenant where the physician undertakes obligations to his teacher and progeny out of gratitude for education. The vow or oath pledges the physician's loyalty to his teacher and a professional guild, and to secrecy. The pupil is adopted as a son by their teacher, as was common among the Pythagoreans of that time. Pythagoras, like Hippocrates, was an Ionian Greek, who gave rise to a cult with religious, political and philosophical interests.

The date of the Oath could be between the sixth to third century B.C. as the Pythagorean movement was capable of preparing such an Oath during this time. The Oath is most compatible with Pythagorean thought, but could have also been influenced from other traditions and cults. The original purpose may have been part of a reform movement to move away from the more dominant medical practices and ethical values of Classical times. The followers of Hippocrates were on the Island of Cos, so it would presumably have been first used at that medical school. Galen said that "in ancient times medicine was in the hands of families of physicians and one had to learn it during childhood, in the case of daily life. But in later times strangers came into the medical profession, and then the good old family teaching, begun in childhood, disappeared, and one needed books for learning as well as for retaining medical knowledge". A transition was occuring around the fourth century B.C. (Kudlien 1968).

There are at least four more major works in the Hippocratic Corpus which are also of unknown origin but specify the good manners that the ideal Hippocratic physician should display. These, together with the Oath, are sometimes called the deontological works. The Greek word for etiquette, *euschemosyne*, literally means being graceful, elegant, manifesting good form or bearing; the Greek word for ethics, *ethika*, means of, or for, morals. There is a subtle difference between them (Carrick 1985), though they usually overlap. For the Greek physician the rules of etiquette were not followed out of fear of civil punishment but out of the love for the Art and the benefit of his reputation in the highly competitive market for physicians. The rules of etiquette were only rules of thumb, never the unequivocal law. In the absence of medical licensure, the financial success of one's practice depended upon the patients' perceptions of the physician only. These works are probably aimed at young physicians.

The *Law* is a short work of 300 words, from around the fourth to fifth century B.C., Jones (1924) suggests it might have been a short address by a head of a medical school to graduating physicians. It complains about the lack of state control upon medicine that allows many quacks to practice, and the absence of no penalties to keep erring physicians in order. It sketches the type of education needed by a good physician, and urges physicians to acquire a real knowledge of medicine, not just an outward show. It shares the ethic of advancing the profession's interests as well as meeting the genuine needs of the patients. It states that medicine is the most illustrious of all the skills, and the last words imply an actual ritual of initiation into a craft or guild (Philips 1987). It also shares the allegiance to the secrecy of medical knowledge within a sect. The last two sentences imply that these physicians were initiated into a secret guild.

The Physician dates from about 350-300 B.C., and includes advice at the end of the work that young doctors should learn surgery by treating war-related injuries.

There are concerns shown for fairness in social relations and opposition to sexual exploitation of patients. There are also directives to do with the proper dress and behaviour of doctor, and also the physical shape and complexion of the doctor, which appear more to do with establishing a good reputation than any ethical recommendations (see Jones (1923) for translations of the Hippocratic works).

Precepts is written later, maybe in the first century B.C., and may have Stoic influence. There is a tension shown between furthering the self-interests of the practitioner and working for the benefit of patients. There are references to fee-setting suggesting that the wealth of the patients should be considered, to seek the fullest possible payment for services, while showing compassion to the needy, "the love of man". It also states you should not discuss fees during treatment. There is a need for a "brotherly" physician to behave well (Jones 1923).

Decorum is of similar origin, and shows Stoic influences, and like the others attacks the work of quacks. There is a utilitarian emphasis attempting to balance the needs of the patient with those of the physician. It also proclaims the grand ideals of the art of medicine, a form of wisdom, to provide for the patient's benefit and to secure for the physician the best reputation and greatest financial success possible. The physician who is the lover of wisdom is the equal to a god. Jones (1924) believes that *Decorum* and *Precepts* are from oral addresses to a secret society, such as a mystery guild.

There is also some advice for good conduct in the medical work, In *The Surgery*, in among the medical procedure. While these writings share the concern for the patient's best interests with the Oath, there is a difference in emphasis as the Oath does not consider the outward concerns for good business of a physician, something which is concentrated upon in the other writings. The Hippocratic work *Prognostic* says that prognosis is valued as it may win the confidence of a patient, as well as for medical advantages and for curiosity. It was necessary to persuade the patient to undergo treatment, when many quacks were present (Jones 1923). Prognosis is a useful device to eliminate the risk of failure from medicine, and protect physicians; but appeal to a code of ethics is better, as any patient can be treated, regardless of the likelihood of successful treatment. He promises to the public that he will do whatever is in his power to save and care the patient, with no guarantee of success.

Both parts of the Hippocratic Oath have been retained in the modern medical tradition. The first part laid out the duties of the pupil in a covenant form. The covenant could be viewed not only in a business but also is consistent with the Pythagorean ideals of brotherly behaviour. The pupil promises to regard his teacher as equal to his parents, to share his life with him, and to support him with money if needed. The pupil is made the adopted son of the teacher. There is a lack of evidence that medicine was normally passed on from father to son in closed family guilds as with other crafts, though it occured among the Pythagoreans (Edelstein 1943). There is still debate over whether the Asclepaids of the Island of Cos belonged to a familial or a more inclusive type of guild. However they appear to have only been local associations, which may of given some sort of status to physicians in the cult of Ascelpius when practising in foreign communities which offered no craft protection. The is not enough evidence to say whether the Hippocratic Oath was taken by the Asclepiads themselves, and there is no evidence to say that they adopted outsiders as members of their families with such a set of obligations

(Edelstein 1943). Later, the prestige of physicians was to come from training in better-known Medical Schools (Bullough 1966), as it does today. More important in the modern contest is the instruction that the pupil must regard his teachers offspring and fellow pupils as his fathers, and teach them the art if they wish to learn it. The brotherhood of the family leads to the formation of a closed profession, which has been adopted enthusiastically by modern physicians.

Philantropy

One of the major motives expressed in Hippocratic writings for pursuing medicine is the love of mankind, or philanthropy. This quality has sometimes been called caring, compassion, humanitanism, altruism or beneficence. Recently the word philantropy has been associated with paternalism of physicians (May 1975, Veatch 1979). In *Precepts* a passage reads "For where there is love of man *(philanthropia)* there is also love of the art *(philotechnia)*". While this can appear to be a lofty ideal (Entralgo 1969), the original meaning of philantropia was the benevolence of the gods for man. By the fourth century B.C. the word was used with a more general meaning of friendliness in reference to personal and social relations, but is still retained the original meaning of a relationship between a social superior and inferior (Amundsen & Ferngren 1982). This philanthropy was very different to Christian charity (Hands 1968). The original passage in precepts occurs in the middle of a paragraph dealing with the question of medical fees, and the philanthropia refers to the physician but philotechnia actually refers to the poor patient (Amundsen & Ferngren 1982). Philanthropy in Hippocratic writings means no more than a certain friendliness of disposition. The verse has been commonly misinterpreted.

A similar passage occurs in the *Physician* which states the physician "must be a gentleman" ...who is "grave and philanthropos". However this does not mean the physician should be a lover of mankind as a reason for practising, but rather to be "kind to all". It tells the doctor to be dignified, not aggressive, harsh, arrogant or vulgar. Both passages suggest that philanthropia is used to designate the proper behaviour of the physician toward patients (Edelstein 1956). Public philanthropy was one of the most important means of obtaining honour in the Graeco-Roman worlds, the motive was not philantropia but *philotimia,* "love of honour". The impulse for giving was not pity (Hands 1968). Archeological work has found numerous public inscriptions honouring physicians for their work. Even in the Hippocratic work Maxims (I) the doctors motive is recorded, that "the quickness of the disease... spurs on the good doctor not to seek his profit, but rather to lay hold on reputation".

By the time of Galen (160 A.D.) there had been a major change in the idea of philantropy, so that it was more inward sympathy for the weak (Edelstein 1956). The ideal of philantropy or love of humanity was the highest professional virtue that a physician could possess. Galen did not invoke the Oath, but he called the best physician the philosopher who is motivated by love of humanity, and cited several historical examples, such as Diocles and Hippocrates, though accepted others are motivated by love of honour, or money, saying the most important thing is their proficiency in the healing arts (Galen I). Galen did understand the idea that surgeons would conceal their procedures to make themselves more competitive, but thought that they should share. A century earlier, Scribonius Largus (40 A.D.) had written

that a true physician "is not allowed to harm anybody, not even an enemy of the state", the sympathy and humaneness of a physician are due to everybody, a philanthropy (Edelstein 1956). Scribonius (I) calls medicine not an art, or science, but a profession in the religious sense, like a vocation, with an associated ethos. The origins of this idea of philanthropy might go back to the second century B.C. in Stoic philosophy, such as Panaelus and Cicero. The most powerful boost was the growth of Christianity, with the idea of charity, as described in the next section.

Do no harm

The duty of the physician to do what they think benefits the patient or to keep them from harm is stated twice in the Hippocratic Oath, and this duty could be called the Hippocratic Principle (Smith 1979). Actually the maxim often claimed to be from the Hippocratic Oath, "primum non nocere," or "at least, do no harm," is not to be found in the Hippocratic Corpus, its origin is unknown (MacKinnon 1988). The principle can be formulated in several ways. The Hippocratic Oath states "but I will never use it to injure or wrong them [patients]", the idea that medicine is a moral enterprise and the knowledge should only be used for healing. Medical knowledge is privileged and should only be used to help, not for malevolent purposes. This idea is certainly found in the Hippocratic Oath, and has been part of the Hippocratic tradition. The Hippocratic work *Epidemics* states "to do no harm," which is a directive to take due care when treating disease. Galen rephrases this maxim "the physician must aim above all at helping the sick; if he cannot, he should not harm them," (Galen II). This puts the "above all" on the helping motive, the reverse of the latin maxim, and is applicable to the idea of thinking of the risk-benefit ratio, at least try to do good. The fourth version is the latin maxim "Primum non nocere," which is on the cautious side, maybe more appropriate to ancient medicine which often resulted in worse symptoms than the injury, but also useful today. If harm is going to come to the patient, there must be some compensating benefit.

The oath describes the proper conduct of the physician, such as to refrain from injustice and mischief, which would be a common ideal, though it does include both women and men, free and slave (Edelstein 1943). Justice is required of the physician, beyond that in the laws of the state. The promise of silence or confidentiality is made a duty, beyond the level of a precaution.

The imperative not to have sexual intercourse with the patient, is in common with other groups also, such as the Stoics, Plato (II), and in the Hippocratic treatise, *The Physician* (Jones 1923). This sort of regulation is also found in the Oaths of other cultures. The Oath also protects the privacy of the patient, secrecy was a feature of Pythagoreans, but it may of been shared with some other groups (Kudlien 1970). Edelstein claims that the prohibition on abortion and euthanasia is exclusively Pythagorean, but this idea is also hinted at in other writings, including Plato (II), that the physician is more responsible for causing death than the layman by virtue of his knowledge (Carrick 1985). The prohibitions followed by "in purity and holiness I will guard my life and my art", which is a demand to religious holiness, certainly not to civil law, or to most philosophies. It is true that among the Ancient Greek philosophers the Pythagoreans are the major group consistently against abortion or euthanasia, believing that they are sins against god.

There were very strict traditions on the visiting of male physician's to women. Gynecology and Obstetrics were largely the area of women, in Western medicine,

until the seventeenth century when male midwifery was introduced. Even when physicians were allowed to attend women for medical consultations there were strict precautions. The Visigothic law prohibited surgeons from bleeding free women in the absence of an approved witness (MacKinnery 1952). The Salernitan treatises of Archimatheus ordered the doctor "not to diminish his professional status by ogling the patient's wife, daughter or maid servants" based on the direction of the Hippocratic Oath. Apothecaries of sixteenth century France had to swear an oath including "never to examine women privately". Medieval Christianity and Islam had very strict views, the exception is the Jewish tradition which does not forbid solitary visits (Jakobovits 1975).

The Oath states "I will not use the knife", which appears to be against surgery, yet there are other writings assigned to Hippocrates that have much useful surgery, so Nittis (1940) suggested that this prohibition relates to castration, by changing the normal usage of one of the verbs. However, this interpretation is not generally accepted. Some scholars suggest that the clause against surgery is a later addition, as it is not mentioned in the oldest manuscript, that of the Christian version of the Oath (Jones 1924). However, Edelstein (1943) rejects the reference to castration altogether, and believes it was intended to be against lithotomy, but applicable to all surgical operations in accord with Pythagorean teaching. The patients which required, or desired, surgery might have been referred to others "who are engaged in that work".

Earlier we had mentioned that the forbiddance of surgery has been interpreted by some as refering to castration (Nittis 1940). Castration was very common in Antiquity, a considerable number of eunuchs were made by physicians. With the advent of Christianity voluntary castration became common, to avoid sensual passions. It was practised by Origon and many patriachs of Constantinople. The early Christian physician Paul of Aegina wrote "Although the aim of medicine is to correct and not to corrupt nature, the physician nevertheless at times finds himself compelled by those in authority to perform castration" (Nittis 1942). The Christian version of the Hippocratic Oath of the tenth century omits reference to this surgery verse, perhaps for this reason. Though the practise was forbidden by various ordinances, Italian parents were known to castrate their sons so that they would remain sopranos, which was only abolished by Pope Leo IX (Cawadis 1946). The 1215 Lateran Council decreed that clerical physicians were forbidden to practise surgery (Talbot 1968). After this, presumably the older form of the Hippocratic Oath would be more appropriate (surgeons and physicians received the same training).

Of much more importance is the promise not to give deadly drugs or abortive remedies to patients. This concerns the physician more in their capacity as pharmacists who possess very powerful drugs. There was certainly widespread abortion in the Ancient World, and infanticide was very common (Eyben 1980). There are many medical writings that refer to abortion methods, and many philosophical arguments were used to support it (Carrick 1985). Actually the earliest references to the Oath are in the first century A.D. by Scribonius Largus (I) in 40 A.D. Though Soranus (I), a Greek physician in Rome in 60 A.D., the most famous of the ancient gynaecologists, disagreed with the Hippocratic Oaths views on abortion, he did cite it, but he thought that it was necessary to think of the mother's life first. Reasons such as the wish to preserve her beauty or to hide the

consequences of adultery he thought were not sufficient to warrant an abortion. The Hippocratic work *On the Development of the Child* does suggest that abortion could be obtained for any reason from many doctors, including that author. Pythagoreans, however, are known to have believed that life started at conception. The Christian version of the Oath extended the ban on supplying abortive pessaries, seen in the Urbinas manuscript of the Hippocratic Oath, to any method of abortion in the Ambrosian manuscript. Apothecaries, like the physicians, had to swear never to administer an abortive potion (Cumston 1926). The Hippocratic Oath was used by supporters of respect for human life in the question of euthanasia also by the second century writer Apuleius (I). It was consistent with the concept of the absolute sanctity of life of Judaism and Christianity (Frankena 1975).

Despite the widespread use of abortion some recent statements on medical ethics cling to the Hippocratic Oath as a basis of medical ethics. The Canadian Medical Association Code of Medical Ethics states that the basic principles of the Hippocratic Oath are retained as basic guidelines. The reason given why physicians who practise abortion, or surgery, are said not to break the Oath is to refer to the preliminary part of the Oath which includes a phrase "I will fulfil this oath and this covenant according to my ability and judgement", which is interpreted in a twentieth century way as allowing the oathtaker to break the covenant if it is in their judgement justified (Kluge 1990). One has to wonder why there is a desire to maintain such an Oath as the expression of medical ethics. It reduces the importance of the oath, and it is better for guidelines to be based on following principles of medical ethics. The desire to make the medical profession appear like it follows long followed ethical traditions does not require the selective use of ancient writings.

The interpretation of giving a "deadly drug" can relate to murder or euthanasia. Poisoning was a common means of both at the time of writing. However, there were already many laws to prohibit murder, so it would be unnecessary to include this in the Oath, it is addressed to the exclusion of euthanasia, the more popular view in this period was the opposite. Plutarch (I) says that Pausanias, King of Sparta from 408-394 B.C. said that the best physician was the man who did not cause his patients to linger on, but buried them quickly. While the aim of medicine was to preserve or restore health, it was not to prolong it per se. This view is also seen in Aristotle (II) and Plato (IV). The Hippocratic treatise *The Art* defines medicine as having three roles: doing away with the sufferings of the sick, lessening the violence of their disease, and refusing to treat those who are overmastered by their disease, realising that in those cases medicine is powerless. The physician was completely free to treat or not (Art I). In Ancient Greek culture, Platonists, Cynics and Stoics, all considered suicide as an honourable alternative to hopeless illness (Daube 1972), and assisting in suicide was relatively common (Gourevitch 1969). Physicians actually gave their patients poisons for which they were asked, and the famous anatomist of the third century B.C., Erasistratus, took poison himself, to end the suffering from cancer. The Hippocratic Oath is as we have seen an esoteric document often inconsistent with the wider picture of Greco-Roman medical ethics. By the second to third century A.D. the Hippocratic idea that it was wrong to aid suicide had spread, though the real influence was probably the Christian belief that it violated the sixth commandment, so that patients should only be given drugs to relieve the pain. However, what is clearly not a Hippocratic idea is the duty to prolong the life of a patient who did not want to live. There was a rising

idea of the respect for life (Temkin 1975), but this was not the same as is argued today, to prolong life. The actual idea to prolong life appears to come from the sixteenth century. Francis Bacon divided medicine into three areas, the preservation of health, the cure of diseases, and the prolongation of life, "the third part of medicine which I have set down is that which relates to the prolongation of life, which is new, and deficient; and the most noble of all," (Bacon I). He urges physicians to find cures for diseases that are incurable, though Bacon supported euthanasia (Amundsen 1978d).

Adoption of the Oath by Western Medicine

It is important to consider the situation in Classical Greece and Rome regarding medical practice. The physician was classified socially as a businessman, occupying a low position in society (Edelstein 1931). Each physician had to prove themselves in a competitive and roving market. There was no system of medical licensure, no professional standards enforceable by sanctions against physicians who were "unethical", no physicians were required to swear any oath, a wide variety of views on ethics were held and that these changed over the long time periods and among different cults (Amundsen 1978a). No group of physicians or school of thought was so dominant as to separate orthodox medical practitioners from heterodox, no monopoly existed (Friedson 1971). Practitioners took patients on at their own discretion and had no special duties to treat people (Amundsen 1978d). If a group of physicians were to follow the strict practices of the Oath they would gain a good reputation which was essential in increasing their clientele among the competition. The lay population of that period faced substantial uncertainty about any physician, but if they were associated with a cult, they would have some sense of the physicians commitments.

The Oath is probably not a legal document, but was voluntarily taken by a few physicians. If the physician of the guild violated the Oath, he would still be able to practise medicine, the only control was a careful choice of members to join their guild, however, reputation was very important in securing business. The motivation to obey the laws of etiquette was for the love of the craft and financial reasons, not the fear of punishment. The word "etiquette" only implies "should", not "must" as the Oath implies, but there was no formal disciplinary body. Jones (1924) suggested that the Oath and other deontological works represent the views of secret societies of physicians. Some of the reasons for this are; the perculiar nature of the Greek of *Decorum*,, which includes strange words and expresses characteristics of the liturgy of a secret society, the obscurity is greatest when the writer is speaking of the "gods", the Oaths regulations for student-teacher relationships and the passing on of knowledge, the *Law* implies a medical course, in *Precepts* (Chap. V) the genuine physician is called one "who has been made a brother". Though there is no conclusive trace of a special cult in *Precepts* or *Decorum*, they imply the existence of some sorts of cults, and they would of had distinct advantages. There would certainly be some advantages in following a reputable teacher or school. Xenophon (I) said that a man who wished to become a "public" physician had to name his teacher and account for his medical training.

There was no special ethic for physicians, the same civil law existed for all

and each could be seen as joining in some elementary social contract to the individual patients. The freedom of medical practice in Greece had left no real control on the profession, in contrast to the state-imposed regulations found in neighbouring Babylonia, Assyria and Egypt. One of the primary elements in the emergence of the Oath and the associated code was the existence of the condition of free medical practice, and the willingness of some physicians to respond by accepting responsibility for their own professional conduct (Carrick 1985). The Oath may have been the start of a reform movement in the later part of the fourth century, to reshape the ethics of the physician (Edelstein 1956). The morality and outward performance characteristic of the Classical era, and reflected in the Hippocratic writings on medical etiquette, was to be supplemented by a morality of inner intention. The Hippocratic works show how a group of physicians was trying to form a profession, and on the other side of the coin, it is easy to see the advantages of forming and belonging to a guild with these aims. The public attitude was different to today also, medicine was not held in high esteem, as it is today, as we can see in some of the comments in the Hippocratic works such as the *Art* or *Regimen in Acute Disease* (Jones 1923), or Plato's comments. The reason for this was the wide divergencies of opinions between different physicians, the many cases when treatment did not cure, and the cases where the disease went away on its won accord; as well as the widespread quackery. The Hippocratic writings try to free medicine of quackery, superstition, and some rhetoric.

Hellenistic physicians often violated its injunctions, yet it was much later to be widely accepted. The dominant view as to why the Hippocratic Oath has so widely been adopted is that these Pythagorean teachings were deemed compatible with Christianity (Konold 1978, MacKinney 1952). However, the small number of early Church Fathers who knew of the Oath, including Tertullian, Cyprian and Ambrose, were generally disapproving of it (Kibre 1945). For centuries following the appearance of the Oath, the medical profession of that time has left no sign that it accepted it. In the early Middle Ages the pattern of physicians was similar. As time moved on it become apparent that there should be some regulation of medicine. The first evidence that the Oath was being taken seriously is the rhetorical discourse of Libanius (370 A.D.) that implies that all doctors must assent to its clauses before practising (Amundsen 1978b). There is also a letter of advice written by St. Jerome (late fourth century) to a priest visiting the sick, in which the Oath is mentioned and some ethical advice given (MacKinnery 1952). Yet its form was not fixed, and its details could be easily changed so that it was adopted by Christians, Jews and Muslims. A major Christian influence was the responsibility toward the poor and the sick, the duty to care was a new concept (MacG-Jackson & Short 1966). Christian charity led to a revolution in the attitude of society toward the sick, as first seen on a large scale in the great plague of the third century (Eusebius I). The first "hospitals" were founded in the fourth century, later they became centred around monasteric orders. After this time there were various versions of the Hippocratic Oath circulating for several centuries (Larkey 1977). Visigothic law in Spain of the sixth and seventh century includes several provisions governing physicians behaviour, including the writing up of contracts with individual patients before treatment (Amundsen 1978c). And in the Ostrogothic Kingdom of Italy, Cassidorus wrote to a physician referring to "certain sacred oaths of a priestly nature" by which medical students were obligated, thought to refer to the Hippocratic Oath (MacKinnery

1952). The practice of medicine in Classical Greece and Europe had always been a right, not a privilege, until the beginning of these geographically limited licensure requirements. We can talk of the medical "profession" in Classical Greece and Rome only in the sense that the phrase designates the people who called themselves physicians (Amundsen 1978d).

It is under the Arabs that the Hippocratic Oath was first administered by a civil power as an entry requirement and guarantee of competence for the medical profession; and where we first hear conflicts between state and doctors basing themselves on the words of the Oath. The first time that medical practice was limited by a major governing authority in the Middle Ages was in Baghdad in 931 (Burrow 1978). Further discussion of the use of the Hippocratic Oath in Islamic medical ethics is described later. The physicians al-Rahawi (d. 925) and al-Majusi (d. 994) both urged physicians to adhere to the Hippocratic Oath, which had earlier been translated into Arabic (Hamarneh 1968). A similar development occured in Western Europe where medical practice begun to be under external regulation by canon and secular law, medical licensure requirements were made, and professional organizations emerged with obligations to the state (Amundsen 1978a). MacKinnery (1952) has summarised some of the eighth to tenth century medical etiquette works. They include topics such as bedside manner, in addition to qualifications and training of the physician, and the spiritual aspects of medicine. There are several ninth century manuscripts from Paris and Chatres which say that the physician should "be mindful of the Hippocratic Oath," and "He who wishes to begin the art of medicine and the science of nature ought to take the Oath and not to shrink in any way whatsoever from the consequences. And then by this process of oath taking let him take up the teachings." There is also an eleventh century manuscript in Copenhagen of Salernitan influence which begins, "Before the physician takes the Hippocratic Oath". These all point to the requirement of physicians to take the Hippocratic Oath at least in some medical schools from the ninth century. There are also some traces of Hippocratic etiquette which are recorded, those these are not a code but a set of ideals.

The major link of the Hippocratic Oath to modern times is the existence of a tenth century manuscript of a Christian version of the Oath entitled "From the Oath according to Hippocrates insofar as a Christian may Swear it" (Jones 1924). There are three old manuscripts, the oldest being the Vatican library manuscript, Urbinas 64, the three versions show much variation in detail, so it is probable that there was no fixed form of the oath. There are many changes made, including:

* pagan deities are replaced by Christian references (2 Cor. 11:31), and God is called on as a helper rather than any swearing by God.
* the pledge of secrecy of teaching is replaced by a pledge to teach the Art "to those who require to learn it", this tends to discourage the formation of a secret organisation or profession, as a teacher should teach willingly without any indenture or apprenticeship agreement. The Christian reviser discourages the formation of guilds of physicians to restrict medical practice.
* the prohibition upon surgery is rejected.
* a stronger prohibition against abortion.

What is retained is the pledge to use treatments to help the sick according to the physician's ability and judgement (Veatch 1981).

In 1140 in Sicily, the King Roger II initiated a state examination for medicine,

"out of concern for safety and welfare of the people" (Sigerist 1960). Emperor Frederick II in 1241 published regulations for physicians, giving a monopoly of medicine to those who passed the exams and were licensed (Frederick II), also adding the obligation to give medical advice to the poor without charge. A nine year course was to be studied including the first three years study of logic, and an oath of loyalty to the state, not to the profession, was taken. This type of legislation may of helped establish the preeminence of the medical schools such as at Salerno. At Salerno and Montpellier students were required to swear the Hippocratic Oath, at least by the year 1181 in Montpellier (Guthrie 1957). Similar legislation was reenacted in Spain in 1283, Germany in 1347 (Veatch 1981) and in Italy in 1365.

Elsewhere in Europe licensure was accomplished by private guilds. The first area of guild development in medicine was in surgery, in France in 1258 there was a guild established (Bullough 1966). There were many guilds in the following century. The growth of guilds partly depended on the increased application of an ancient body of medical ethics and partly upon legal sanctions. These guilds had the right to make and enforce standards of quality in their products, to limit competition between members and to limit entry into the profession. They attempted to hold a monopoly on service and training and licensing. The medical guilds stressed the dangers of quacks to the public, using the argument that quality control was essential for the common good (Cosman 1973). They were to monopolise the practice in larger towns, and any practitioners outside of the guild would be arrested. In certain places medical guilds promised free treatment of the poor, but the Christian obligation to care for the sick had been lost. The Physicians had again become businessmen, intent on making a living, and much of the writings of physicians in Middle Ages concerns fees (Amundsen & Ferngren 1982). The craft guilds developed their own ethical codes. The members of the guilds gained a monopoly, and the public gained safer medicine (Friedson 1970).

The role specific duties for physicians were grounded in civil law, a type of social contract. By the fourteenth century there was a highly developed professional code, with its principles taken mostly from Hippocratic writings, further building on the centuries of writings which had been the Hippocratic ideal (Welbourn 1938). The Oath was printed in the *Articella* by the sixteenth century, translated into Latin as the *Iusiurandum* (Kibre 1945), as was the *Law*. Also among general medical writings there are comments on etiquette. The Hippocratic legacy continued. The Oath was very frequently printed in Elizabethian England, together with interpretations. By 1600 medical licensing was the norm, and physicians were publicly accountable, and medical schools began to assume a position of greater importance within the University than other faculties (O'Malley 1968). The Oath was one of the first parts of the Hippocratic Corpus to be translated into English, though there had been earlier Latin versions. There are at least four different translations of the Oath in the sixteenth century, which give different interpretations to parts of the Oath (Larkey 1936). The relation of the student to his teacher is given broader meaning. The ideal of treating the poor is added to the Oath, which had been seen in the much earlier Christian and Muslim versions. Newton (1586) included in the Oath, "that I shall not be squeamish to bestow my skill upon the poor and needy, freely and without fee". The Oath was considered in an almost legal sense, and held to improve the art of medicine as an ideal to aspire to.

One of the most important developments in medical practice was to be the

emergence and organisation of the medical professions. These corporate bodies were the forerunners of the Royal College existing in Britain, and similar bodies in other countries. They provided regulatable professional associations, a forum for the discussion of various problems including the ethics of medicine, and they published agreed codes. The Paris medical faculty published a code in 1452. In 1552 the Royal College of Physicians (RCP) of London drew up the *Dtauta Moralia*, their local ethical code. Many more codes were formed in the eighteenth century, when there was a large growth in the number of physicians and hospitals. The physician of the eighteenth century was very individualistic, and competition arose between them for patients and the use of hospital beds. There was much abusive writing between them (Wilkinson 1988).

There was an interrelationship between the development of medical ethics in Britain and America. In the period 1765 to 1865 there were more values changes in the character of the physician/physician, physician/patient, physician/community relationships, and in medical education. Three British physicians who contributed to this change are John Gregory (1724-1773), Thomas Percival (1740-1804) and Michael Ryan (1800-1841) (Burns 1974). Percival was asked in 1792 to draft a code of rules to regulate and govern practitioners at Manchester hospital, after many conflicts between physicians, surgeons and apothecaries there. Gregory (1773) had believed in a thorough education in ethics for physicians, but Percival did not, rather he laid out many precepts about transactions between the members of different guilds, all with the aim of increasing patient care. Ryan was to produce a manual of medical law and ethics. He stressed how any society should incorporate its values about professional behaviour into civil statutes which impose legal obligations on professionals. Percival's code at the beginning of the nineteenth century retained the core of the Hippocratic tradition (Percival 1803, Waddington 1975), though recognising surgery as an honourable art. The principle concern is with professional etiquette, cautioning physicians to display respect for one another, avoid criticism of colleagues, and to conceal any professional differences with other physicians from the public as this would lead to a degrading of the medical profession. Doctors should work to enhance public respect for the entire medical profession.

These three works were widely read in America also. The main American work was by Benjamin Rush (1794) who included an appendix to a medical work which he called *On the Duties of a Physician*. He had attended John Gregory's lectures while in Edinburgh. He was described as the Hippocrates of Pennsylvania. The first American code was made in 1808 by the Boston Medical "Police", using the second chapter of Percival's book (Burns 1974). There were other state codes copying this, and some that also includes Gregory's ideas. This code was adopted in 1847 as the code of the American Medical Association (AMA). The situation in 1847 was one of crisis in the United States as there were many "quacks" who were competing for patients. Exponents of this code of ethics hoped that the public would cooperate with the doctors in establishing good standards. The code required orthodox training, and forbid advertising (Konold 1978). The next major work in medical ethics was the book of the American, Hooker (1849), interpreting the AMA code. The British Medical Association (BMA) tried to formulate a code, but it took them more than ten years. In 1858 the British Government passed a medical act, under the influence of the BMA. This set up the General Medical Council, which was entrusted with the legal regulation of medical practice and the oversight of

professional conduct. In 1887 it issued the first statement on professional misconduct, but only after World War II did it deliver extensive guidelines on professional conduct.

The most significant revisions to the AMA code since then have been in 1957 when the detailed set of rules was replaced with a set of ten guiding principles, which was principally based on the World Medical Association (WMA) code, while retaining the warning against professional associations with "unscientific practitioners". They obligate the physician to expose the legal and ethical violations of other doctors. In 1980 a patient's rights perspective was introduced (Veatch 1981). Other non-Hippocratic factors have been introduced such as to take into account the interests of the rest of society, the physicians rights and duties, and the need to consider the judgement of the patient and other health care workers. The WMA (1948) has tried to retain an updated Hippocratic Oath with "the health of my patient being the first consideration", colleagues to be treated as brothers, and the physician is to maintain "by all means in my power, the honour and the noble traditions of the medical profession". It attempts to make the original Oath fully applicable to modern conditions in a pluralistic world. It does offer a basis for professional pride and solidarity. The international profession was formed.

There are various oaths still in use. In the United States 90% of medical students swear an Oath, while in Britain very few do, and some Schools, such as Cambridge or Durham, have never administered the Oath (Guthrie 1957). The Edinburgh medical school has an oath, but it omits the obligation to the teaching of future students and the respect for life. Similar abbreviated forms are sometimes used elsewhere (Wilkinson 1988). The modern Oaths usually share the Hippocratic ideas of doing no harm and to practice confidentiality, and often include respect for life and for teachers. There are also codes, which are statements of the principles of medical ethics, such as the WMA code or the AMA code. Different associations such as the World Psychiatric Association or International Council of Nurses and the International Dental Federation also have codes. Also the WMA has various declarations concerning the treatment of human beings, regarding experimentation (Helsinki 1964, 1983 update), determination of death (Sydney 1968, 1983 update), therapeutic abortion (Oslo 1970, 1983 update), torture (Tokyo 1975, 1983 update), patient rights (Lisbon 1981), and the right to refuse extraordinary treatment (Venice 1983).

Competing Ethical Traditions

We should examine some of the competing traditions, which are often at variance with the Hippocratic tradition We may better understand why the Oath has been retained, and question whether it still has a place in the future. We should look for universal features which are appropriate for medicine today.

Judaism includes guiding regulations for appropriate behaviour for physicians within Jewish Law, both the rabbinic tradition or Talmud, and the Torah. There is a description of peoples proper attitude to wise doctors written about 180 B.C. in the Old Testament Biblical book, *Ecclesiasticus* 38: 1-15. It describes a physician who conscientiously practises his profession and is an agent of God. This attitude is found in Judaism, Christianity and Islam. Around the fifth to seventh century A.D.

the book of Asaph the physician, the oldest known Jewish medical textbook was written. At the end is an Oath which he and his colleagues administered to their pupils at the end of training, called the "Oath of a Thousand Words", it reflects some of the articles of the Hippocratic Oath: (Rosner 1977). The pagan gods and goddesses of ancient Greece are replaced by Yahweh, the physician must follow the commandments as in the Law of Moses. There is more emphasis placed on the character of the physician and his need to trust God, while working as God's agent. A principle ethical code is the codification formerly ascribed to Moses Maimonides (1135-1204), but now believed to be the work of an eighteenth century Jewish physician Marcus Heuz (Rosner 1967). Unlike the Hippocratic Oath, but in common with some codes, such as the ancient Chinese code, there is the idea of helping the poor and needy (Veatch 1981). A key feature of Jewish Law is the overriding value and sanctity of human life, rejecting any Hippocratic, Christian or Modern compromises (Jakobovits 1975). The duty to preserve life is the dominant obligation, and this is reflected in their medical ethics. It does share the commitment to healing and the relative unimportance of patient rights. There is no Jewish version of the Hippocratic Oath itself. The omission may be due to the strong aversion to swearing an Oath, much stronger than the Christian adversion. It seems that Jewish students were not exempted from swearing an Oath during medical training, which may of even prevented some Jewish students taking their degrees (Jakobovits 1975). The Hippocratic Oath made less of an impression on the Jews than it did on the Christians and Muslims, as Jewish law lays down special moral qualifications only for religious officials. Physicians must follow the regular rules, such as respect due to teachers, protection of human life, laws against euthanasia and abortion, sterilisation and chastity.

Catholicism has had historical points of contact with the Hippocratic tradition, though early Christianity showed little awareness of the Hippocratic cult, and the neo-Pythagorean mystery cults were often explicitly rejected by early Christians. In the fourth century Greek and Christian thought converged, and Jerome does refer to Hippocrates but not to the Oath (MacKinney 1977). The traditions remained separate during the Middle Ages (Amundsen 1978b). The physician's role model is Christ, not Hippocrates. There are five basic principles of Catholic medical ethics, those of stewardship of the body, inviolability of human life, the principle of totality, of sexuality and procreation, and the principle of double effect (Veatch 1981). There are many Catholic Hospitals and Medical Institutions which are instructed to follow the Catholic ethical codes, which differ principally from the standard Western codes with regard to reproductive questions and abortion. Modern Protestant medical ethics is based more on viewing the relations between the patient and the physician as a covenant (Ramsey 1970), than the sharply formulated principles of Catholic moral theology (May 1975). Christian codes regard beneficence, such as striving to do the best for the patient and avoiding harm in the Hippocratic ideal, as a command which does not just apply to the patient but an active duty to all people.

Islamic medical ethics was largely formulated during the ninth and tenth centuries, while Arab scholarship was at its zenith, with influence from the Hippocratic corpus (Ullman 1978). Islamic medical tradition has dual sources from scripture and the Hellenistic world. What was to emerge was not a dichotomy but the growing Muslim civilisation developed a mixed approach of drawing on other values, the way of "adab" (Nanji 1988). This balance was framed in the ninth

century work *"Practical Ethics of the Physician"* (Levey 1977), which actually was written by a Christian, Ali al-Ruhawi. This was a 223 page book and describes the desirable characters and etiquette of a physician, such as he must be sensible, learned, pious and act without haste, and have faith in God. He later goes on to explain the "dignity of the art of medicine", which means that the physician must be honoured above royalty. Doctors are held in very high esteem by the public, and medicine is considered a noble profession. Complaints are generally not voiced (Asper & Haddad 1978). They do not require the Hippocratic Oath, as an oath is not needed as the profession was given by God only to those who are qualified. He writes that Hippocrates wrote the Oath so that people could study medicine more as it would not be limited to hereditary sons. Al-Ruhawi says that there are many quacks in his time so he advocated examinations. Following this, there was further writings, with much Hippocratic influence, and his countryman, al-Majusi, urged the taking of the Hippocratic Oath (Hamarneh 1968). In the thirteenth century an Arabic version of the Hippocratic Oath is found in the *Lives of Physicians* written by Ibn Abi Usaybia (Jones 1924).

Modern Islamic ethics uses a system based upon moral law as recorded in the Koran and the Hadith, and is basically "Allah's will be done", very different to the Hippocratic tradition, though there is still some influence. Islamic medical ethics is gaining importance because of the number of Muslims in the world and the greater desire to follow the Islamic lifestyle by them (Rispler-Chaim 1989). All contraceptives are permitted, in keeping with coitus interruptus, which had been practised already by Muhammed. Intentional AID is considered as adultery. If an explicit reference to the classical sources of Islamic law cannot be found, then it may be considered in the light of "public benefit" (Maslaha).

Hindu medical ethics are different to the Christian or Islamic approaches. There are some oaths, including the Oath of the *Caraka Samhita* from the first century which is structurally similar to the Hippocratic Oath (Jaggi 1978). The Oath of commitment to the teacher is actually much stronger, and after this are some moral teachings. There is also an instruction to pray for all creatures, and a list of people not to be treated including enemies of the king or the unusual or those of immoral conduct or those on the point of death. The directive to leave dying patients without medical help is not found in the Hippocratic Oath (Etziony 1973), but is seen in some Hippocratic writings. There are also instructions on good etiquette as well as ethics. The code is linked to the idea that ill health is because of bad behaviour in this or past lives (Veatch 1981). Since the thirteenth century there has been influence from Buddhism and Greco-Arab influence which led to *Yunani* medicine, which has a code similar to the Hippocratic one. The Indian philosophy also includes the idea of do no harm as one guiding principle. Indian medical ethics today includes Hindu and Western influences, plus many folk traditions and other religious groups. The present code of physicians conduct in India dates from one made in 1956 to replace the Hippocratic principles introduced by the British (Jaggi 1978).

The urgent problem in the third world is the very low number of physicians and medical resources for such a large population (Desai 1988). This leaves new problems such as to decide on the relative priorities of preventive and curative medicine, something not solved by medical oaths. Medicine may only treat those who can be successfully treated as there are no enough resources to treat all.

Modern secular philosophy is quite different from that of either Hippocrates or religious ethics, and within the last decade has led to the emergence of the concept of patient rights (McCullough 1980). The patient rights movement, a kind of consumers movement, encompasses a broad coalition of those unhappy with the paternalism of medicine, including abortion rights activists, critics of the professional domination of medical research, and advocates of the freedom of choice for or against treatments for the terminally ill (Veatch 1981). The American Hospital Association (1972) formulated a "Patient's Bill of Rights" which included these concerns and within several years this was adopted into law by U.S. Government agencies. The Parliamentary Assembly of the Council of Europe (1976) adopted a recommendation "On the Rights of the Sick and Dying" which also states that the patient has the right to refuse medical treatment. These are significant departures from the paternalism of the Hippocratic doctor. The responsibility for the development of medical ethical guidelines is shifting from the physician to society as a whole.

Socialist medical ethics also involves using oaths, for instance the "Oath of Soviet Physicians " (1971), which replaced the Hippocratic Oath. The pledge of loyalty is changed to the service of people and for the interests of Soviet society. This is in contrast to the Hippocratic Oath where the physician must work for the sole interests of the patient. In socialist countries the right to personal health care is also stressed. There is still some residue of the Hippocratic tradition among Soviet physicians however.

Chinese medical ethics involves the convergence of Confucianism, Taoism and Buddhism (Unschuld 1979). There is a struggle between professionalization of medicine and the control of medical resources, and concerns regarding the relationship between the profession and lay people. In the seventh century Sun Simiao wrote "*On the Absolute Sincerity of Great Physicians*," sometimes called the Chinese Hippocratic Oath (Qiu 1988). Among the commitments are equality of treatment, attempts to save all creatures, and not to seek wealth. They should regard physicians as equal to patients, and not publicly criticise other physicians as this only leads to jeopardising the public image. He mentioned that some of the public thought that physicians were greedy, so they should not appear to care about money (Unschuld 1979). The Confucian scholar Lu Chih (754-805) urged similar virtues, of humaneness and compassion, stating that the medical resources must be distributed fairly among the population. Every family should have someone with medical knowledge to be able to care for their relatives. Medicine was not to be practiced as an occupation but as part of humaneness, without a fee. The Taoists and Buddhists, revised this with the concept of "Great Physicians" who possess special knowledge and responsibility, thus creating an elite, along with the Hippocratic ideas of keeping professional secrets, and the brotherhood of physicians. In China, as in the West, there were some physicians who wanted to call one specific system proper and to demand the outlawing of heterodox concepts. The codes of ethics appear to have been initiated by individual practitioners for the benefits of public respect as well as humaneness, but professional organisations were unknown in Eastern societies until this century, leaving it up to individuals (Unschuld 1978). There is a strong emphasis upon the virtues, including the concern for equal treatment of all classes, with writers such as Kung T'ing-hsien in 1615 attacking those physicians who had reduced medicine to a profession. It is historically

interesting that before the communistic ideal of the last few decades there has been a long history of the idea of equality which is not found in the Hippocratic tradition which addresses behaviour to the individual patient only. They do share the concern for a prohibition on killing, and the two sides of ethical behaviour, to do good and not to do harm.

Japanese medical ethics is a mixture of Buddhist and Confucian influences combined with Shinto influence. From the fifth and sixth century the medical profession has been restricted to the privileged classes. With the centralisation of government in the seventh and eighth centuries there was a bureau of medicine established, with the Yoro penal and civil codes creating an official physician class. Because of shortages of doctors there was room for some others. After the Heian period (800-1200) the government-sponsored health service was replaced by professional physicians. In the sixteenth century a code of practice was drawn up that is very similar to the Hippocratic code, called the Seventeen Rules of Enjuin (Kitagawa 1978). The code requires that physicians should always be kind to people, and devoted to loving people. There is a very strong paternalistic attitude by doctors even today (Ninomiya 1978). Among the code of Enjuin is the directive to keep the Art secret, and to form a brotherhood. There was concern about quacks also (Takemi 1978). The most important issue in Japanese medicine today is the paternalism, that means for example, that 90% of the doctors will not tell their patients if they have serious cancer. In a situation where patients are not aware of their disease, the question of informed consent seems a distant issue.

Retaining the Hippocratic Oath

As we have seen, there is a very wide variety of different practical ethics exhibited by different doctors. When problems in medical ethics arise, many Western doctors first turn to the Hippocratic Oath or its modern analogues articulated by organised groups of professional physicians reflecting the Hippocratic tradition. However the Hippocratic tradition is often in conflict with other traditions as illustrated. In some countries the Hippocratic Oath is so widely used that the possibility of changing it has not been considered, only minor changes made (Levy & Ohry 1987). However, there are many medical ethicists who suggest that we should change the idea that an ethic for medicine can be based on a professionally articulated code. There is a complex set of understandings between the professional and society so a contract theory has been suggested by many (Veatch 1981). There has been a growing body of writing suggesting that medical ethics fundamentally involves social relationships among lay people and health professionals built upon complex layers of mutual loyalty, fidelity, respect, and support (Pellegrino 1973, Magraw 1973, Brody 1976). With this at the backs of our minds, let us consider new genetic technology, and resume this discussion in the final chapter of this book.

5. Status of the Human Embryo

The debate over the status of the human embryo, with all its promise and potential to develop into a human life, has been central in the debates on abortion, methods of birth control, IVF and scientific experiments. These discussions in public often result in separation of people who view the embryo as of protectable status, and those who will consider other factors may allow the use or destruction of embryos. It should be apparent that this chapter is not going to change this situation, however, what we should all know is some details of embryonic development, and other factors which affect public policy. The next section considers scientific experiments on embryos. The reasons why they are performed and an international comparison of legislation and regulations. A final section on fetal tissue transplants is included.

The arguments concerning the status of the embryo at different stages of development, which affect the way we consider an embryo, are discussed at first. Before considering these technologies it is important to discuss the status of the human embryo.

Human Embryonic Development

The human embryo is formed from the fusion of a sperm and an egg at conception after which it undergoes a series of complex and as yet poorly understood stages in the development to a human adult. The gametes are produced in the testis and ovary of male and females. The series of cell divisions is delicately controlled, and the result of these series of cell divisions is to half the number of chromosomes in the germ cells, from 46 to 23. The steps in this process are represented in figure 5-1. After penetration of the egg by the sperm, the nuclei of the sperm and the oocyte fuse, and the chromosomes align, in a process called syngamy. It is here that a new genotype is formed. There are numerous accounts of the process in more detail, in most biology textbooks, or in books discussing the status of the human embryo in more depth (e.g. Ford 1988).The important subsequent steps in embryonic and fetal development are summarised below, in Table 5-1.

Figure 5-1:Schematic Representation of Gametogenesis and Fertilisation
The sequence of cell divisions in the formation of sperm and oocytes are illustrated with the chromosome numbers are written in italics.

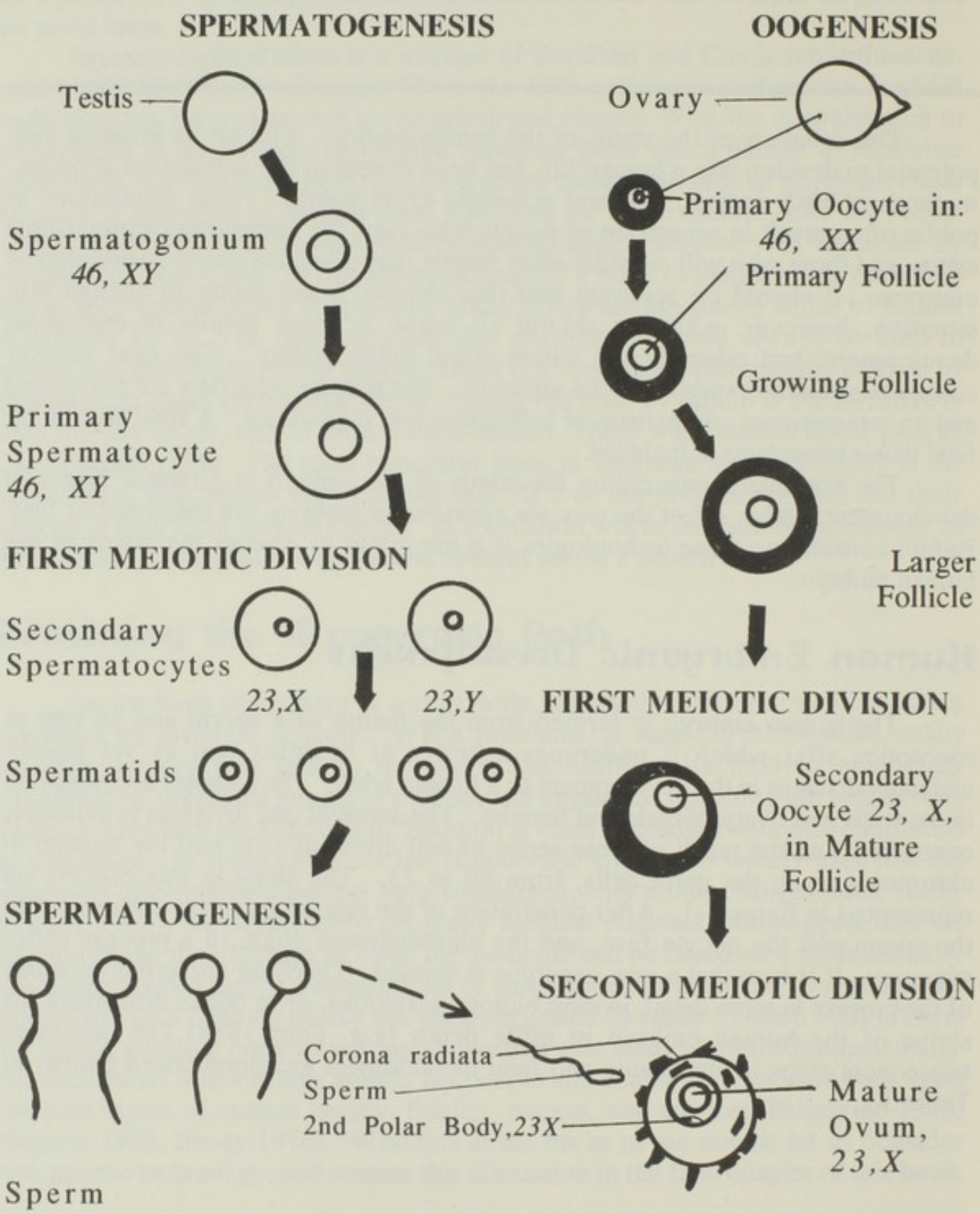


Table 5-2: Important Stages in Human Embryo Development

* There are about 300 million spermatozoa in a single ejaculation.

* Conception, the penetration of the egg by a sperm is followed 22 hours later by syngamy, the alignment of paternal and maternal chromosomes to form the the new genotype.

* At 2-3 days, or the 8-cell stage, probably every cell is totipotent.

* 45-70% of "preembryos" do not successfully implant.

* Can predict identical twinning at day 7, and by day 10 they are forming individual embryos.

* Up to 14 days the embryo may develop into a cancerous tumour (hydatidiform mole), or two embryos may recombine to form one individual.

* At 14 days implantation is complete.

* After 14 days the primitive streak starts to form,one per individual

* At 8 weeks the first neural cells start to be differentiating, and the name changes to fetus.

* By 12 weeks, about half of the embryos that implanted may have spontaneously aborted (about 80% since conception).

* By 12-16 weeks the fetus has taken on a distinctively "human" form, and may feel pain or respond to stimulation (not necessarily the same thing, as brain dead people also have some responses from the spinal cord).

* At 17-20 weeks quickening occurs.

* By 22-24 weeks viability is reached, in some cases, if in good hospital.

* At birth severely handicapped newborns may be left to die if the parents do not want extraordinary treatment to proceed.

Ethics through Embryo Development

One could commence this discussion with the question when does a human life begin? Many people have thought of possible answers to this. In fact the question should be more carefully stated, as there are different meanings possible, which are relevant to the status of the human embryo. In this section we will consider alternatives, from conception to birth.

Human life, as commonly termed, is constituted through the union of the sperm and egg. In western religions this life is endowed with a particular form of "life", or soul, by God. The central issue then becomes when this created means of our relatedness to God and other humans appears, is it emergent or is it inseparable from the conceived embryo. In Islam there are identified stages, the fetus becomes a person when it receives its soul from God at the end of 17 weeks (though it is not right to create life in order to destroy it, that is God's domain). This perceives human life as an individual, which is the common belief among peoples of most cultures and countries at the end of the twentieth century. This view is in contrast to the view of traditional eastern religions, which believe in long sequences of continuity, death being merely a means of transition to a new outcome, until you break outside of the cycle (Bowker 1986). This view of human life considers it more as a species than individual lives, but together with other living organisms. However, for the discussion of the status of the human embryo, the more useful approach, and certainly the more relevant to most people, is to consider the question from the viewpoint of the individual. The question of human identity is also complex in itself, there are genetic, bodily, spiritual and social identities which are intertwined (Kjessler et al. 1989).

Modern medical embryology has been interpreted in two ways. One approach is illustrated by the current Roman Catholic view, which considers that at no stage of fetal development there is a significant reorganisation to indicate that a major qualitative change occurs before which the fetus could be identified as not ensouled, and after which it could be considered completely ensouled (Iglesias 1986). So in the absence of such a critical moment one is left with the idea that the fetus has been ensouled from conception (Vatican 1974). The argument of genetics supports this, since following fertilisation the full genetic blueprint of a new individual is created, which may begin to develop (though the first few weeks are more under the developmental control of the egg, the natural process is embryonic development). One could also say that the Bible verse Genesis 2:7 can be interpreted to say that, "man became a living being (soul)", does not imply that he was entered by one, but it is quite inconclusive in meaning, even for Christians. The original meaning of the word "conceive" refers to the woman receiving the seed in her womb and becoming pregnant by taking the fetus to herself. There are various linguistic expressions for conception, but they do not answer the question of when a human individual comes into existence (Ford 1988). During the past century the process of fertilisation has come to be associated with conception.

The other interpretation of embryology stems from the pioneering experimentation and philosophical interpretation of Aristotle. His view was that there was a biological development of the early embryo through several intermediate stages of growth, considered first to be vegetative, then animal, and then at 40-90 days after conception, the human was sufficiently organised and disposed to be the recipient of the specifically human form, the rational soul (Aristotle III). The influence and content of Aristotelian reproductive biology has been discussed by Ford (1988). Thomas Aquinas extended this view, maintaining that our flesh is conceived before it is animated. In the case of a subject which was not suitably disposed, God would not ensoul them. This view was also held until the last century by the Roman Catholic church.

Fertilisation

People agree that the new human life begins at conception, or in the following twenty four hours, when the genetic information from the egg and sperm join to form the new genotype. Although the egg and sperm were alive, they were not a new life. We could also say that the unfertilised egg or the sperm that does not join an egg, will perish so can not be considered the start of a human life.

Most people agree that a fertilised egg, an early embryo, is of a higher status than two gametes alone, the egg and sperm, though the consequentialist approach (Kuhse & Singer 1982, Singer & Wells 1984) would say that the fertilised egg and gametes are indistinguishable. Fertilisation does not begin life, life in terms of a living cell is continuous. The egg cell, or oocyte develops from the germ plasm, and is inherited across generations. The patterns of early embryonic life are laid down prior to the trigger of fertilisation. Fertilisation establishes a new genotype, and activates the oocyte to develop into a embryo. However, the developmental program of the embryo can be activated by some agents without fertilisation taking place. The precise time of fertilisation can not actually be pin-pointed within a 2-3 hour period, so it may be difficult to measure the time of this change in status, but it still occurs. It can be philosophically distinct despite our inability to measure it.

During the recovery of eggs from the ovaries of women prior to IVF or GIFT it has been found that as many as a quarter of them are activated, and are developing parthenogenetically. Parthenogenesis is where the egg is activated without the presence of sperm. The high frequency is not thought to be because of the treatment, but is thought to occur naturally (Braude 1989). The moral status of a parthenogenetically developing egg, which has no potential for further embryonic development, is equivalent to the unfertilised egg. There may be several cells, but it is still different to a fertilised egg which has potential to develop.

The life of a 1 cell embryo is not sacrosanct, and has never been, even in theological circles (Dunstan 1984, BSR 1984, 1985). The current Roman Catholic view does have doubts, and does not categorically state that the human soul is present from conception, despite the genetic material being present (Vatican 1974, 1987). However, in the absence of certain knowledge it views embryo experimentation or abortion as wrong as it is taking the risk of killing an ensouled human (Mahoney 1984). It may still be held that developing human life is inviolable, irrespective of whether it has an immortal soul.

The First Two Weeks

There are several major difficulties with the view that ensoulment, or personhood, starts at conception. A high percentage (perhaps 70+%) of fertilised eggs do not naturally implant, or result in a live birth (Leridon 1977). Most failures occur during the first few days, including fertilisation itself during which many abnormalities, mostly chromosomal in nature, occur (Murphy 1985). It is argued that this is a very inopportune moment for ensoulment to occur (Gardner 1972, Dunstan 1984, Jones 1985, 1987). The actual embryo at this stage might not even develop into a human being, but instead form a hydatidiform mole, which develops into a tumour. This is the argument of wastage, and it is a significant one. Critics note that in cases of infant mortality which is as high in many countries, as was in earlier times here, but in this case we don't say that a newborn infant is not a human

person. Often the cause of pregnancy loss is genetic, but genetic disease kills people throughout the human lifespan.

Many scientists refer to the embryo before two weeks as a *conceptus* or *pre-embryo* (Huxley 1985), but for the sake of this discussion there is no need to introduce more words into the moral debate, as words may be biased in there use (Chargaff 1987). After consideration of the issues we may consider this term appropriate.

While a new genotype is formed after fertilisation, the genetic information does not appear to be significantly used until the 8-cell stage. Before this the egg cells use existing genetic messengers (mRNA). The egg cell has inherent natural capacity to direct and organise its own self development for several cell divisions. The maternal and paternal genetic information is differentially used, the paternal information is used to make the membranes around the embryo itself, which result in the placenta; and the maternal genetic information is used for early embryo development but not for placental tissue. This is despite the fact every cell has the same genetic information, half maternal and half paternal. Depending on where the cell is in the embryo different genes are used.

Not all the cells in the early embryo differentiate into the fetus, the placenta, chorionic membranes and umbilical cord also develop, and these are discarded. In animals, any cell isolated from a 4-16 cell embryo can redevelop to form complete individuals, clones. Animal clones have been made by this method (Willadsen 1986). The individual cells in the embryo do not behave as a individual embryo until after the 32-cell stage, when intercell connections start to appear, and the morula forms. The cells are kept together physically by the zona pellucida, a thick surrounding coat, as they travel towards the womb prior to implantation. Cells can also be removed for genetic analysis, while the remainder of the embryo can develop normally, this has been used for preimplantation genetic diagnosis (see chapter 13). Human embryos share most features of embryogenesis with other mammals. Though some aspects of gene expression and determination are not common to all species, such as brain and nervous system development (Williamson 1986).

In the process of IVF, if it is known that the embryo is abnormal, e.g., those possessing 3 pronuclei at fertilisation, it should not be replaced into the mother. The potential is for this embryo to grow as a triploid fetus and child, grossly abnormal, or to even transform into a growth in the mother's womb (like a hydatidiform mole which develops into a chorioepithelioma, a fatal tumour) which would threaten her life. The placental abnormality of a hydatiform mole, is usually found to arise when all 46 chromosomes are of paternal origin only, thus only placental tissue develops, no embryo. A teratoma is a cancerous growth, and can form at various stages. In this case it would be wrong to replant, as it is potentially a hazard to the mother, if not for only consideration of the possible child.

The embryo can form two genetically identical embryos, twins. In some cases two embryos can combine into one, which can become one individual (Mahoney 1984). The process of twinning depends on the place were cell division in the early embryo occurs, and what determines this process is being investigated.

Implantation and Formation of the Primitive Streak

After implantation is completed there is much more biological stability. If ensoulment occurs at a fixed time after conception, it is probably after this stage,

though the argument of predestination (God creating a person) could be applied at any stage in the process. However, it seems that ensoulment should only occur when there is an unambiguously individual subject. In an important book in this area, Ford (1988) argues that the criteria for the presence of a human individual is when the living individual has the inherent active potential to develop towards human adulthood without ceasing to be the same ontological individual. He places this around this time because of implantation and the formation of the primitive streak. At the time of completion of implantation the cells in the embryo start to differentiate in a process called gastrulation. By 19 days, three layers of cells that are going to remain separate for the development of different tissues are forming. The neural tube starts to form, and a primitive circulation system is forming by the end of four weeks. The formation of the primitive streak occurs at 14 days, and is a major sign of ontogeny. This concept of individuality is shared by some scientists, such as McLaren, and some theologians such as Mahoney or Ramsey (Ford 1988), and by the Warnock Committee (HMG 1984). This is why the 14 day stage is important in government guidelines in several countries.

There is one note of caution however, regarding the use of incomplete scientific data to set guidelines. The argument that twinning occurs at 14 days was also used to support this time, however, recent data suggests that twinning can be detected at 7 days, and individualisation at 10 days (Edwards 1989). Ford makes a negative claim, that a developing mass of cells cannot be regarded as a human individual until the formation of the primitive streak. However, this bases human individuality on current scientific data, but the embryo may be biologically destined to be an individual before this time, but we are unable to detect this. The beginning of an individual could occur prior to this. However, the arguments of stability of the implanted embryo prior to primitive streak development remain powerful.

The Fetus and Feeling Pain

At about 8 weeks the embryo is called a fetus, as it takes on a recognisable form. By 12-16 weeks the fetus has distinctive "human" body characteristics. By 12 weeks, about half of the embryos that implanted may have spontaneously aborted (about 80% since conception). In some studies, two thirds of spontaneously aborted fetuses between 2-7 weeks have been shown to have the wrong chromosome number. If the implantation was a multiple pregnancy, it is very likely that some of the embryos will of been aborted, in one study of 25 multiple implantations, only four sets of twins were born, and the seventeen single births, the rest spontaneously aborted (Barron 1985). These observations are important, and suggest that after implantation there is continued selection of fetuses, much of which has the end result of aborting abnormal fetuses. Further research is needed to study the factors which cause a mother's body to reject or retain the developing fetus.

The ability to feel pain is also important. There can be two general types of moral significance. There is intrinsic moral significance when an organism can feel something, such as pain. It has a greater intrinsic moral significance when it can be self-conscious. This is different to extrinsic moral significance. Some things can be of high extrinsic moral significance, but have no intrinsic interests, and this depends on circumstances. To a fertile couple, sperm and eggs are of little extrinsic moral significance, many are wasted during life. However, to an infertile couple a single

egg can be of high extrinsic moral significance. An embryo can be of high extrinsic moral significance, but it may not have intrinsic moral significance until it can feel something. To a person of particular religious views some act may have high extrinsic moral significance, but the same act to another person is of no concern. If we are forming public policy than acts of high intrinsic moral significance are more compelling than those that only involve extrinsic moral significance to a proportion of the population. Until, an embryo has intrinsic moral significance, in a pluralistic society the public policy should represent the difference between the types of moral significance and public opinion.

Personhood

What is a Person?

Since this book is written by and for human beings it is clear that the status of human beings will be a major question to consider. The actual term "human being" is an abbreviation of the legal term "human in being". We must decide when the life of a human being begins. A central issue in developing an ethical framework in which to examine issues involving human life is to examine if there is a difference in the way we regard different human lives, and to examine what we mean by a "person". There are two basic approaches that have been used in discussing questions of life and death. One centres on whether it is ever morally permissible to take the life of any human person; and draws parallels between abortion, warfare, self-defense and capital punishment. The other centres on asking the question of what constitutes a human person, and ranges over the issues of brain death and permanently comatose patients, abortion and the quality of life. The discussions are often very emotive, but it is a controversy which needs a rational decision, and not simply dogmatic utterances. We must ask whether we view ourselves as a member of the human species, or as a person. In our common experience, all the persons we communicate with are human beings, but there are several cases of chimpanzees that have been taught how to communicate with us, in some limited way, we need to ask whether we consider them as persons. Philosophically it is safer to use the word person, than to use the term human being. This point is often argued when discussing animal rights (Singer 1990). For the purpose of this argument we should use the term person. I consider the subject of animal rights in chapter 6.

A person is generally referred to as someone who is rational, capable of free choices, and is a coherent, continuing and autonomous centre of sensations, experiences, emotions, volitions and actions, these are what may be called the characters of a person. The word person, has two ideas. The Anglo-Saxon reductionist philosophy produces the idea of a person as something which acts in certain characteristic and identifiable ways. The other philosophical approach, has its roots in ancient Greek thought which has had a powerful influence on Christian thinking, goes behind the observable phenomena and activities to identify their sources, the nature of these sources and the relationships between these natures (Mahoney 1984). It stresses being more than behaving. The Greek idea is present in Christian speculation and language about the human soul. When a "human" possesses a soul they are a person. In Christian terms a human person is someone made in the image of God, which is not dependent on a criteria of actions. A human

person may be more than human cells with the potential to become a human person (Mackay 1979, Jones 1985). We would all agree that the human person is entitled to protection and respect. No human person is property, and all have equal status.

There are several aspects of a human person. The word person comes from the Greek 'persona', meaning an appearance or face, an individual appearance that has continuity through a story (O'Donovan 1984). An individual becomes an important part of our ideas, as does the idea of the soul. Human beings change with time and experience, in a way persons grow, creating themselves. We change especially when born, as we become rational, self-aware, and through our childhood as we learn or are moulded. We also change when aging at the end of life, such as with disease. We have some of the responsibility for what we make of ourselves (Macquarrie 1987). However, in order to change our personality we have to be a person already, so while it is important as persons to be able to learn from experience, does it mean that if we lose this ability to change we are not persons? Human beings could be thought of as embodied spirits, though in a non-dualistic way. There may be limitations imposed on us by the world, or our body, or our current existence, however we can be persons despite these. Being human often implies a capacity to experience both limitation and freedom.

Our dialogue between persons, social interactions are important. Our selfhood only finds its growth in social relationships, we are made fully human by our web of social relationships. However, if a person loses the capacity to communicate with others, but can receive sensory input, we still consider them a person. If they lose the capacity for self-awareness in the usual way, but have split brain personalities, do we regard them as two persons or one?

Another crucial part of our person is self-awareness, or personal identity. Personal identity is important, so that even if an exact replica was made (Gillet 1987) we would have two persons, and if the original died,they would still regard themselves as dying. Our experience of the physical world is centreed upon ourselves, and specifically around the sites of our senses. Each individual may reach a point where they are self-aware (Harre 1987). Though this view has important extensions, as nonhuman animals can be self-aware, and also higher apes can interact with humans in this way. For instance in experiments using chimpanzees, they can be taught sign language and then they can create short sentences in conversation. Beings can also be treated as persons in a linguistic way, by names, and by ascribing emotions. Parents can do this as they interact with their infants in terms of psychological attributes that they assign to the infant, and we may do this to domestic animals too.

The Soul and Ensoulment

Before considering the origins of personhood, during our development, we should consider some aspects of thinking on the human soul, as this would seem to be the essence of a person. One of the important reasons for Christians, Jews and Muslims to place a high value on human life is the belief in the soul (Ward 1985). Each person is precious and unique because they possess a soul, a spiritual status. Although nonreligious people may not accept the word, soul, many share the view that members of the human species have a higher status than other animals because of the same characters associated with what Christians will call the soul. The body, soul and spirit of the human individual are not separated, all are integral in a

Christian view. All human life is not the same, although it always has a derived worth, derived from the value given by God. Human dignity comes from our creation in God's image. The person is both a moral agent and subject.

For as long as man has known of the soul there have been ideas on where it is located, and whether it is in the body as a whole, or in the heart, or air that we breathe, or liver, or brain, or some combination of these. This thinking has moulded our concepts of what is essential to human life, and is relevant to the questions of when we believe human life or personhood begins and when it ends. This is because most human thought has made the soul paramount over the body; the "wise" soul has been considered superior to the "foolish" body. Twentieth century thought would give the brain prime importance, as it is the only organ that is largely irreplacable. Many of the features of the human brain are being understood, and while it is extremely complex, it is commonly assumed by some sociobiologists that eventually human personality will be reducible to neurophysiology. Conscious behaviour has a neurophysiological basis, and can be affected by drugs, surgery or electrical stimulation. There are some important consequences of a mechanistic brain, the idea of "free" and responsible persons may be replaced by the image of a machine, however, the influence of environment and genes in shaping our behaviour, will mean such a view is not compulsive. The brain may be understood to a fine degree, however it is still possible to view it as a free agent. The body is uniquely the body of this brain and no other, as the brain is uniquely the brain of this body and no other, but parts of the body may be transplanted, except for the brain - though nowdays the brain cells may be transplantable.

The locus of death is related to the position of the soul. We could ask the question where we look to see if a person is dead? While being concerned with the death of the individual as a whole, different concepts of death had led people to consider different body functions and structures in order to diagnose the death of a person as a whole. The loci corresponding to the irreversible loss of vital fluid flow are the heart and the blood vessels, and the lungs and the respiratory tract. The Greek, *pneuma,* meaning both breath and soul, illustrates where the loci of death were. With modern life-support machinery, the locus corresponds more with the loss of capacity for bodily integration, the central nervous system and the brain. This concept includes the unconscious homeostatic mechanisms and the higher reflex mechanisms like spontaneous respiration and pupil reflexes. This does not necessarily give the human soul a loci or substance, as Wittgenstein said "the human body is the best picture of the human soul", a human being needs a capacity for physical functioning of some sort. Karl Barth viewed the difference between soul and body in the theological context of reflection about the human being Jesus Christ and the experience of God's Spirit (Barth 1942). He calls the human being "the soul of his body", a literal translation of the Aristotelian/Thomist definition *anima forma corporis.* The soul rules, the body serves; the soul dominates the body.

The timing of the beginning of the human individual actually coincides with the time of ensoulment. The soul is not necessarily associated with a material structure. The only characteristic biological substratum which the infusion of the soul requires is a new human life, which exists from conception. The origin of the individual soul has perplexed philosophy since Plato and Confucious. The metaphor of ensoulment was used to explain how the individual person does not

originate from its parents, but primarily from outside as a directly creative intervention from God in each case. The Christian position however, is not Platonic dualism, it is more the integrated Aristotelian view. Body and soul are not two separate "things", but two aspects of the same individual. The soul is infused by God in the act of creating each individual human person, since the soul has no material parts, it is either present fully or not at all, it is not a developmental process. Yet it is believed there is no intermediate in the animal kingdom, while it is difficult to comprehend, if the soul is from God then it is not necessary to envisage intermediates (Teilhard 1963), but the threshold can be crossed in a single step, between animal instinct and human reflection. Matter and spirit are not totally disparate though, as God who is spirit, created matter, and did so essentially for the sake of spirit and orientated towards it.

Human ideas about the soul, or self, have changed over history. At one stage, breathing was the most important, with a person being alive in the rhythm of their breathing. The pulse of the heart became important, and the heart was seen to be the centre of the emotions. From the Alexandrian medical school in the third century BC the brain was known to be the centre of the will and the powers of reason, though for some period this knowledge was lost. The location of the soul has long been thought to be with the brain, and for the last two centuries with the thinking activities of the cerebral cortex. The soul is generally no longer viewed as some dualist being, as it was in Ancient thought, but is connected much more with the thinking, the rational, or part of us that makes us people, which is attached to the living cerebral cortex, though people continue to remain divided on the question of immortality. There is still divided opinion whether the whole brain is involved, but this seems to be moving more to exclude the mere brain stem, the part we share with all animals, to involve only the higher brain, parts of which we share with the so-called higher animals.

Brain death is a recent term, and is still not accepted by some countries as an alternative to cardiac arrest such as Denmark, and is still being debated in others, such as in Japan or India. In countries where brain death is accepted as being able to be detectable, the philosophical debate has moved again to the site that we place the soul, where human reason is located. The debate is whether human death is signified by the death of the higher regions of the brain alone, the cerebrum and neocortex, even if the brain stem is alive. The higher brain is concerned with the content of consciousness, while the brain stem must be alive to generate the capacity at all for consciousness (Lamb 1985). Some draw distinctions between "alive bodies", "persons", and "corpses" (Agich 1985). There could be alive bodies that contain persons, and alive bodies that are brain dead, that do not, yet it may still not be a corpse. The body of a comatose patient may not be alive in the sense of being the embodiment of a person, though to relatives the warm body may still contain the soul of the dead. We have to decide whether death is socially constructed in its definition, and whether it is the death of a human person that is the crucial element. It is the role of a physician to determine when life has ended, and if we adopt these criteria there is an important role for science in deciding when life begins.

There are still strong feelings concerning the moving heart as it remains the most visible vital organ. This association faded from philosophical thought with the advent of understanding of the central nervous system, several millenium ago, but the heart has remained the verbal and visible sign. There has been a very

considerable time lag between of concept of where the soul is, to our concept of the locus of death; however, part of this could be accountable by the lack of technology available to measure brain death. Linguistically, we may still talk of our heart, some languages, such as Japanese have different words for the emotional and physical heart, but in English the word has multiple meanings. While we may scientifically be able to define death, the definition of death of a person may remain socially defined (Veatch 1989), and different people may accept different criteria. There are legal problems if we retain differences, but these are greatly exasperated at the other end of life, the beginning. While we can respect different peoples views when they deal with themselves, if they involve what is seen as another human being, the fetus, it becomes much more difficult. Some legal standard is necessary, that reflects peoples differing views plus scientific evidence.

The Beginning of Personhood

During fetal life the characters of personhood are apparent in increasing ways. We can examine the different stages in embryonic development, and fetal growth. We can look back in our lives and consider whether there is some point at which we can say that we became a human person. It is clear that the biological qualities of personhood are not present at conception, what is present is something we call the embryo (I use this term rather than conceptus or preembryo), but it does not manifest the activities of a human person. It is a potential human person, at the biological level at least, rather than a human person with potential.

To function as a human person a brain is needed, and in a parallel way with brain death the criteria used by some is brain life (Mackay 1979). The concept of brain birth was stimulated by the development of the criteria for brain death, in changing the way we define a living human being (Van der Vyver 1990). The concept of brain birth is a mixed one, and has been placed at various points between 12 days and 28 weeks gestation. There are different parts of the brain. Hominisation can be related to the development of the cerebral cortex. Teilhard de Chardin argued that the human species had transcended itself by a major leap in the development of the cerebral cortex, and without it, no specifically human attributes are possible (Teilhard 1959). Bernard Haring asked the question, whether "a living being could be a person at all without the development of the biological conditions and/or presupposition of person life?" (Haring 1972). He noted that the anencephelics with their lack of a cerebrum are incapable of any personal activity.

There is controversy over the status of anencephalic babies, which with the shortage of organs available for transplantation into children, are being used as organ donors (Nolan et al. 1988). These babies have no higher brain, and a new term has been proposed to consider them as "brain-absent" (Harrison 1986). They can neither feel pain or be self-aware, so they lack any self interest in being kept alive. Since they are brain absent they are not even in the category of brain dead, suggesting that it may be ethical to use them as organ donors. There are strong arguments that we should introduce the concept of brain life, as the beginning of the individual (Engelhardt et al. 1989). In West Germany they are declared still-born at birth. If this is accepted it would further strengthen our society's statement that the soul is located in the brain, and in the neocortex to be more precise. We may maintain their bodies respectfully, as we would for brain dead adults, and use organs for transplantation. What may prevent this is extrinsic moral factors, like the

reaction of relatives to this.

There are several ideas in these arguments. The emphasis is on a point in development when brain tissue begins to function. The appearance of a cerebral cortex provides a physical site for personhood, or a soul. The cerebral cortex develops in the period of 25-40 days of pregnancy. An alternative to the cerebral cortex formation is the establishment of a functioning nerve net at 40 days gestation. One measure of a functioning nervous system is a positive EEG signal which represents electrical activity in the brain, which occurs at about 8 weeks. The completion of brain structure at 12 weeks. The soul is the subject of moral and rational consciousness, so some argue it does not exist before consciousness begins. This view leads to the idea of the soul beginning to exist between the completion of neural tube at 3 weeks, at the beginning of brain activity, or with the first conscious experience. The experience could be of many types, but some sort of experience. At this stage the embryo could be said to be of a different kind of being, a conscious being. Before that there have been differences in the type of being, but now there is a different kind. The appearance of consciousness has to be distinguished from the awareness of sensations such as pain. The brain develops gradually, so it is difficult to mark a particular time when a sudden change occurs. Most brain developmental pathways have begun at 24-28 weeks gestation, and this is another possibility (Jones 1989a). Brain birth is a major criteria for personal origins.

Another view is that birth itself is the time of ensoulment, such as that taken by Gardner (1972) from a literal translation of the Biblical verse Genesis 2:7, "God breathed the breath of life into man". However, one could also argue that at the time Genesis was written the breath was a crucial part of the soul, but now we associate the soul with something which appears earlier. Birth has the advantage that it is easy to define. The child that is born is the same developing individual as was in the mother's womb, birth alone does not confer human individuality or personhood. If babies are born prematurely, they can still be viable, but this can occur at very different times. The chance that birth occured at six months and the infant is viable suggests that individuals born at nine months have some individuality, though a different degree of dependence on the mother. Rather than using birth, the important stage is viability (Campbell 1985), and many countries have legal limits on abortion around 22-24 weeks, the maximum viability using modern technology.

An extreme argument is that rationality is the criteria that distinguishes human persons. This may not be noted until many months after birth. Rationality allows people to form relationships, which themselves are very important (Berry 1987). Some philosophers have argued that since a person needs to be rational, and the human infant only appears to become rational after 1-2 years, then they are not persons until them. However, this is a very narrow sense of the word person, even if newborns have not developed to the stage of acquiring the ability to exercise selfconscious rational acts, they are still legally a person, and certainly exhibit self interest. This is normal human experience. It is understood that the infant has an inherent natural active capacity to develop to the stage of being self-conscious and acting rationally while retaining the same ontological identity as a human individual (Ford 1988).

Workable Criteria Respecting Embryo Status

The current attitude of society is that there is a steady and gradual unfolding of life and a gradual assumption of rights by the embryo. The murder of a newborn is as serious an offence as the murder of an adult. From the mystery of human existence we will have respect for creation, whatever our philosophy. We can reflect on the status of human life at several stages of development, and we may be lead to conclude with some degree of moral certainty that human personhood is not ascribable to early stages of embryonic development. However, the intrinsic promise and potential contained means we will treat it with very high regard. Human beings can not treat each other as means to ends but only as ends, but the duties owed to a one cell embryo are not the same as those due to a newborn child, or adult.

When we think of justice we think of the law. We can think of the cases of moral thinking which have been "decided" by making a new law. New laws can have a major effect upon our behaviour and attitudes, well thought out laws are necessary. It is nice to have laws for our "conscience" as it makes things black and white, however some areas are clearly grey and will remain so for the foreseeable future, and we must accept that. This is something that we do not know, and should not claim to, when motives and complex factors dependent upon the situation are involved, in some areas some sort of situation ethics is appropriate. This does not mean that there is not also a class of events which may be seen to be morally wrong but which are to remain legally permitted in a pluralistic society, for reasons that will be expounded such as that of human dignity and freedom of decision making.

From the reasoned argument based on biological knowledge, and ethical principles it is possible to draw different lines in the status of the embryo at fertilisation, implantation, formation of the cerebral cortex, and viability. An early embryo is a body in preparation at least, and the likelihood of homicide increases with the age of the individual. As Mahoney (1984) says, we may not be able to say "this is where I began", but we can say "from this early embryo I as a person took my origin".

I will discuss embryo research in the next section. The embryo may constitute an individual prior to the formation of the primitive streak, at 14 days. This would challenge the boundary that has been placed at 14 days. The argument of the *in vivo* stability at 14 days, following implantation remains important. We will consider the details of laws protecting the early embryo, or preembryo, in the section discussing scientific research on these embryos. It is also relevant to contraception, as discussed in the next chapter. Prior to new chemical tests, it was never possible to show a woman was pregnant until she missed her period, about 14 days after the conception of any embryo. It was only after the advent of scientific research on these embryos that lawmakers started to consider the legal status of preembryos.

There are sufficient doubts over the commencement of human personhood until the cerebral cortex begins to function, not to consider the embryo a person until at least 8 weeks and possibly up to 24 weeks. We await further scientific knowledge. Before this period, the status is lower than a human person, and should be recognised as such in law. After this period, the next clear mark is viability, and

during this period the fetus takes on the status of an individual human being. Our scientific data does not allow any finer demarcation than this. As previously stated, a society may put earlier limits to protect the human embryo or fetus because of social or religious reasons, but they will not do so because of scientific reasons.

Abortion Laws

The mention of the word "abortion" can insight great argument. In the United States it has been a key political issue for the past decade, until recently the Republican party was unanimously against abortion. In the USA the two groups of people that represent the opposing views are often called "pro-life", those who are against abortion, and "pro-choice", those who support the freedom of the mother to decide to have an abortion. The groups are both politically powerful, and make rational discussion of the issue very difficult. Fortunately, in most other countries, although people may hold strong personal views, they have not tried so hard to force their views onto others. I will not dwell on this debate, except to observe that it is probable that in most societies there will remain people of these views, some of whom viewing public policy contrary to their own view, as wrong.

A summary of international abortion laws with respect to the time limits placed on fetal age is presented in Table 5-1. As stated, there are very different criteria used, this summary is only to illustrate how important to most countries abortion laws consider age to be. For more serious conditions, abortion at older age is permitted. In most countries fetal handicap is considered more serious condition, but this attitude is not universal. In Japan, among some groups, there is more acceptance of social abortion than selective abortion for handicapped fetuses because of concerns that this selection will lead to bad attitudes to handicapped people. However, to Europeans these ideas can be dissociated. In Islamic countries such as Egypt or Kuwait, the maximum limit is 17 weeks, from Koranic decree, but strict criteria are applied to any abortion until that time. In Hungary there is a sliding scale, so that the increasing likelihood of fetal handicap from 10% to 50% chance increases the fetal age limit from 12 to 20 weeks of pregnancy (Hungary 1986). In some countries the age limits and abortion laws are under continue review and debate. In Australia the state abortion limits range from 14 weeks in the Northern Territory to 28 weeks in Victoria and South Australia. In the USA the state laws are much more complex, and also changing.

Table 5-1: Comparison of Fetal Age Requirements in Abortion Laws, Note that the criteria to satisfy these requirements for legal abortion widely vary.

Country	Law	Limit (Time in weeks after Conception, ? indicates uncertainty) for indications:				
		Demand	Distress	Rape	Handicap to fetus	Maternal Risk
Australia	State Laws	14	28	28	28	28
Belgium	1990 Bill	12	12+	12+	12+	No Limit
Canada	No	-	22?	22?	22?	22?
Denmark	#350,1973	12	22	22	22	22?
France	#79-1204, 1979	10	10	10	No Limit	No Limit
Germany	#15, 1976	0(in East 12)	12	12	22	No Limit
Greece	#1609,1986	12	19	19	24	No Limit
Hungary	1986	12	12	20	No Limit	No Limit
Islamic Countries	General, Koran	0	<17	<17	<17	No Limit
Italy	#194, 1978	13	13	No Limit	No Limit	No Limit
Japan	#1948	24	24	24	24	24?
Nederland	1981	13	24	24	24	24
Norway	#66,1978	12	12	18	18	18
Spain	#9,1985	0	No Limit	12	22	No Limit
Sweden	#595, 1974	18	18+	18+	18+	18+
U.K.	1990	-	22	22	No Limit	No Limit
U.S.A.	1973 & 1989 court, future?	12	20	20	20?	20?

One argument that can not be used against abortion is that it is a very risky operation to the mother. Although there are occasional fatalities, many more if done without state control, the statistics show that childbirth itself is more risky, with a much higher fatality. The actual likelihood of problems depends on the individual women and the situation.

In most religions there is much concern about abortion. To be morally consistent, if the embryo is considered to be of full protectable human status at a certain time, than if at any period after those dates the living embryo is aborted the death of an embryo is unethical. This is an argument which stands, even if we bring other factors to bear, as an absolute moral principle stands absolute.

It is not inconsistent, for example, to prohibit human embryo experiments after 14 days, but permit abortions until 12 weeks, because in the case of abortion the mother's interests are involved. An embryo *in utero* has the potential to develop into a human embryo, which is something an embryo still *in vitro* does not clearly have. The factors relating to the parents, principally the mother, require

consideration, but they should not be given priority once the embryo has protectable human status. What they can determine is whether the abortion of an embryo/fetus before this stage is ethical or not. There is an increasing recognition that fetuses should be regarded as the second patient. This will increase as fetal surgery increases. The fetus makes claims for a right to nutrition, protection, and therapy (Blank 1984). The mother also has important claims, as the raising of a fetus and child requires considerable devotion. These interests must be balanced, and it can be argued that until the fetus has intrinsic moral significance, that the mother's serious interests can overrule the fetal claim for nutrition.

The situation can be further complicated by advances in the practise of multifetal pregnancy reduction. This is also called selective termination of pregnancy. The birth weight of babies from a multiple pregnancy is lower, and they often have significantly lower chances of survival. As discussed earlier, it is possible that the majority of multiple pregnancies are naturally reduced to one fetus, which is probably a reflection of the increased chances of a single fetal pregnancy. This process can be performed at hospitals, especially for those pregnancies with more than two fetuses. In one set of 85 cases of triplets or greater, 80 were reduced to twins, of which most gave birth (Lynch et al. 1990). Given the enhanced chances of survival and normal life, it may justify the use of reductive abortion. It is an alternative option to parents, especially when the numbers are very high and premature birth is very likely, with the high probability of abnormality; or the other option of total abortion.

Some have suggested that there is a need for national guidelines for this procedure, such as restricting the procedure to pregnancies of three or more fetuses. However, it is unlikely that this procedure will be abused, and it should not be forgotten that most of these pregnancies are found in women who were using drug treatment or assisted reproductive techniques in order to satisfy their great desire for a child. They are going to want to protect the fetuses that they have undergone extensive therapy to conceive. To respect the woman's autonomy, any selective termination of pregnancy within the time limits for general abortion should be permissible (Overall 1990). In fact, there is more ethical justification than many reasons for abortion as this is designed to enhance the survival of the remaining fetus(es).

Some Christians believe that all conceptions are known by God and that He wills them all to develop to their full potential, in which case there is no room for human interference in the process, however this view would seem to ignore human freedom. This is especially obvious in cases of the abuse of human freedom, such as rape cases. Most Christians place strong restrictions on the type of abortion which is viewed as ethical. In Hinduism it is an offence to kill the fetus, as it is a sentient being. The belief is that the process of continuity is co-terminous with conception (Bowker 1986). There is much concern in Buddhist religion also, in Japan there is a ritual like a funeral for each dead embryo, called a mizugo prayer (Miura 1983), as life is seen to start from conception. In Islam, the views differ on whether abortion is legal before 17 weeks (120 days), but in most Muslim countries abortion for serious fetal handicap is possible prior to this time.

If we were able to find an absolute moral principle saying that to kill the fetus is murder, than it would always be unethical to kill the fetus; however, this type of principle does not emerge from a study of the status of the embryo, even if it may

generally be considered unethical to kill a fetus. The quality of man, the soul, his essence, his unique individuality, with its associated dignity or reverence means that man has a sanctity. However, we should not contend, as some arguments against abortion do, that existence is a good in itself as all other goods depend upon it. Some types of existence are not, and especially if there is no person, than there is no spiritual existence.

A working policy needs to consider many consequences and compare these with some basic rights. In a pluralistic society, no one religious view may be accepted for public policy, rather a view that attempts to accommodate and be consistent with the major public opinions, including religious, cultural values and scientific evidence and rational secular philosophy. Different approaches are possible in similar countries, as evidenced by the different laws. Some countries permit abortions, others do not. Many countries allow abortion at later stages of pregnancy if the fetus is shown to be suffering from a genetic disease or is handicapped. There are also differences in contraceptive policies, and embryo research regulations.

The law in Britain was changed in mid-1990. A brief discussion of it illustrates ideas that are common to other countries when deciding public policy. The previous law permitted approved abortions up to a time limit of 28 weeks after the last menstrual period, which is the time of viability stated in the 1929 Infant Life Preservation Act. The new law separated the abortion law from the Infant Life Preservation Act, and reduced the time of viability to 24 weeks, due to the modern techniques for neonatal life support. This was in line with the recommendations from the Royal College of Obstetricians and Gynecologists. In actual fact, the number of cases is very small. Out of 160,000 abortions in Britain in 1988, only 23 took place after 24 weeks, and 19 of these were due to fetal abnormality. The new law will not change the situation much. The actual age after conception is 22 weeks, because in Britain the time is counted from the last menstrual period. There are potential problems for countries that link abortion limits to the age of viability because as our technology advances over the next few decades the age of viability will be lowered. More importantly, although premature babies may be saved, they may not recover to live a normal life. In Britain in 1985, only 9 out of 58 babies born and treated at 24 weeks, survived beyond 4 weeks life. Those who survive are exceptional cases, and may have serious physical and mental retardation. In practise many countries place weight limits, such as 500 grams or higher, as the minimum before that premature baby may be treated. Even at 910 grams (two pounds), there is a high incidence of handicap among such babies. We must know reasonable limits to impose advanced technology in medicine, the same as we do at the end of life.

A more controversial decision in Britain, was the separation of the Abortion Act from the 1929 Infant Life Preservation Act. This means that a doctor is exempt from the new 24 week limit where an abortion is needed to "prevent grave permanent injury to the physical or mental health" of a woman or where there is a "substantial risk of serious fetal handicap" (Wood 1990). This decision was welcomed by doctors, as although there are small numbers of these abortions, they are very stressful for patient and doctor if they are unsure of the real law. However, the exception will apply to a tiny proportion of abortions, and people favour early abortions.

There is a trend in Europe for the liberalisation of abortion laws, even in strongly Catholic countries such as Spain and Italy. Abortion is still illegal in the Republic of Ireland, but elsewhere certain types of abortion are legal. The time limits vary widely, as seen in Table 5-1. West Germany and the Netherlands have liberal laws. Britain is fairly liberal. The most restrictive abortion law, outside of Ireland, is in Italy, where abortion on medical and socio-economic grounds is permitted only up until 12 weeks.

In the USA many states want to ban all abortions, and in July 1990 the state of Lousiana passed such a law. The 1973 Supreme court decision in the case Roe versus Wade protected a woman's right to privacy by granting a constitutional right to terminate pregnancy before the fetus is viable. Up until 12 weeks, abortion is available upon request, during the second trimester a state can regulate abortion to protect the mother's health, but a state may ban abortion in the third trimester, except if the mother's life is in danger. In 1989, the Supreme Court upheld a Missouri state law limiting abortion to 20 weeks. The Louisiana law will directly challenge the Supreme Court, though it may be several years before the law has finished challenges through the state courts. During this time the law will not be in effect. The composition of the Supreme court has been deliberately adjusted over the last decade, to introduce new members who are against abortion, thus the balance of views is very different to 1973. Rather than abortion being only an ethical issue, it has become a political issue in the USA, and the results are impossible to predict at this stage.

Scientific Research on Human Embryos

As a result of IVF there are numerous spare eggs, and embryos. The ownership, and fate of these embryos is one of the major questions arising from the use of IVF. There are also many eggs that have been taken from women being sterilised, and increasingly they have donated the eggs for scientific research. These eggs can then be fertilised to provide a large supply of human embryos for scientific research.

There have been many experiments performed on animal embryos created by IVF techniques, or embryo transfer. Similar experiments could be performed on human embryos. However, genetically manipulated embryos may not be implanted with the intention of producing a baby, because of laws in most countries. Human embryos have be cultured *in vitro* for at least 14 days (Williamson 1986). After this stage they cease dividing in culture, and there is research required if human embryos are desired to be grown past this stage *in vitro*.

Experimental Goals of Human Embryo Research

Most of what we know about mammalian embryos comes from *in vitro* growth of them (Austin & Short 1985). There are some studies which are said to be urgent, such as research into urgent clinical treatments, for the treatment of infertility, the alleviation of genetic disorders, detection of the causes of human anomalies, analysis of the relationships between embryonic and cancer cells, and the development of fetal tissue for use in transplantation (Edwards 1985, 1989). The meaning of scientific research on human embryos is generally misunderstood within

even the scientific community. Some studies can only be made on early embryos. There are different types of research, they can involve observation only, with no damage to the embryos, such as the testing of different culture conditions. There is research on dead embryos, and experiments involving the destruction of living embryos. The report of the British Interim Licensing Authority (VLA 1989, ILA 1990), which regulates IVF clinics and embryo research, approved 53 research projects involving human embryos in 1988-1989. 41 were aimed at improving IVF, 11 at preimplantation diagnosis, and one experiment was to study the development of new contraceptives.

Alleviation of Infertility

The goal of recent embryo research was aimed at successful alleviation of infertility, and has now led directly to the births of many children by IVF. There are many experiments being done in direct connection to clinical uses of IVF (Vines 1987). The first experiments on early embryos were a necessary prerequisite to the technique of IVF (Steptoe 1985). The preimplantation embryos needed to be studied before being used clinically, especially the cell nuclei and chromosomes, to ensure that they were normal. Only after numerous studies of animal embryos were some human embryos studied to see their resistance to noxious agents, and manipulation that was needed for IVF. The procedures for safe fertilisation and transfer for implantation were studied.

There have more recently been many embryos used in the development of conditions for freezing of embryos, cryostorage, which has now yielded births. About half of the patients undergoing IVF treatment have embryos frozen, but only half these embryos currently survive the process. As a medical technique, IVF is best used by taking many eggs in one operation (Trounson & Wood 1984, Edwards 1985, 1989). These eggs are then frozen until needed. The procedure to remove eggs is complicated, and involves a period of hormonal stimulation of egg maturation, so it is easier, cheaper and less traumatic to take all the eggs that can be recovered (may be 20) at once. The better laboratories only need to replant 2-3 embryos to have a reasonable chance of a successful pregnancy. In fact a limit of three embryos implanted per cycle is enforced in some countries to lower the risks of multiple pregnancies. If it is unsuccessful, another set of embryos will be replanted at a later date. The overall increase in the efficiency of the IVF procedure due to freezing is about 15%, but new methods are being developed (Wood 1988). Low temperature storage of human embryos is one means used to improve the clinical success of IVF, as it avoids the need for repeated oocyte extractions. There are also methods being developed to improve the freezing of unfertilised oocytes.

Many experiments are aimed at the improvement of *in vitro* embryo growth. An example of this type of research is the use of "spare" embryos (judged as unsuitable for freezing because of poor quality) in coculture experiments. The embryos were grown for five days on a layer of kidney epithelial cells to determine whether this provided a better medium for embryo growth. Epithelial cells from the kidney are similar to epithelial cells from the genital tract. There was significantly higher growth of cocultured embryos, many continuing development (Menezo et al. 1990). This type of culture system makes it possible for longer *in vitro* culture so that frozen embryos can be grown to the blastocyst stage (5-7 days), and frozen then, as the success rate of freezing has been found to be highest at that stage.

Currently IVF techniques are unable to treat severe male infertility, such as when the sperm are immobile, or in too low a concentration. An alternative is to use mechanical injection of sperm nuclei into the oocyte, or chemical or physical methods of fusing the egg and sperm membranes. This might allow fertilisation with only one sperm (Wood 1988). So far the only method tried on animals is drilling a hole in the eggs' zona pellucida, the thick coat around the egg cell, to allow the sperm to enter (Gordin & Laufer 1988).

The egg cells, or sperm, may be used in interspecies fertilisation tests, but the hybrids are not grown past the early cleavage stage. The interspecies fertilisation test (Aitken & Lincoln 1986) is where oocytes of different species, with more easily obtainable eggs, are fused with human sperm, to test fertilisation. It is preferred to use eggs from other species to test sperm functions, rather than fertilisation of the human oocyte. This would be useful in measurements of male infertility. There is debate as to whether a hybrid embryo is of lower status than a human embryo at the 2 to 4 cell stage, but the normal 2-4 cell embryo is generally accepted to be of low status. There are various types of hybridisation, or chimera production, that are possible, which provide information about the way genetic information of maternal and paternal gametes are used, and the interaction of different embryonic cells.

The production of any human/animal hybrids or chimeras should not pass beyond the stage where the primitive streak is formed, though in practise most would not survive beyond the 2-4 cell stage. The situation regarding chimeras of different human embryonic cells is unclear, but should only be used if it is going to be a therapeutic advantage to the individual made. It is possible that this situation could be reached in the future, though the technology for making chimeras has existed for several years.

Toxicity Testing

They can be used for testing human cell sensitivity to drugs or for carcinogen testing. Embryos could be used to test the effects of newly developed drugs or substances that may possibly be harmful, toxic or cause abnormalities. If done on a small scale where other ethical alternatives are not available, this might be ethical. It should not become commercially routine, but on a small scale would seem to be the best alternative in some cases. The presence of embryonic cell lines might be a preferable alternative and should be possible, so that embryos would not need to be considered.

Embryo Splitting

There needs to be experimentation to examine the question of embryo splitting. This requires the judgement of what is desirable. As discussed above, this would be used to increase the number of embryos available for embryo transfer when few have been obtained after IVF. Extremists distort the use of embryos, from the many possible real benefits of research. A scenario the extremists suggest is that cloned embryos could be grown up and put into a "research park" to provide spare organs to the favoured "twin". This would be recognised as an abuse of science by almost all, and is not a research goal. By the time it became possible much easier alternatives for organ transplantation should have been developed. The clone would be regarded for what they were, another human individual

With recent advances it is possible to genetically analyse a single cell removed

from an early embryo, within several hours, prior to implantation (Handyside et al. 1989). Preimplantation diagnosis will be discussed in chapter 7, it is an area of active research in several countries, and the first babies have been born after its use.

Human Development

If there are many people suffering from currently incurable diseases and disorders that may be cured after the results of work on early embryos, the use of embryo experimentation could be seen as the just decision in an imperfect world. It does not call for indiscriminate research, but after carefully designed animal experiments it may be necessary to do pertinent human experiments to clarify and understand fundamental biological diseases.

Related to the clinical uses are experiments to study embryonic development (Vines 1987), including optimisation of conditions needed to grow embryos as long as possible in vitro. There is a large supply of human eggs and sperm available, so these experiments are not limited by material supply. Developmental genetics will be unlikely to get a high priority in the immediate future, as there are many experiments to be done in animal models before contemplating the "need" for human embryos (Weatherall et al. 1986). Others claim human embryo research is needed for research into congenital diseases now (Williamson 1986) as animal experiments have already been performed. There are many medically useful questions to answer, such as why twinning occurs, how different cells start to form different parts of the embryo and development of tissues (Edwards 1989). There is undoubtedly much knowledge to learn, but preliminary research should be restricted to studies with lower animals. There are many similarities between human and mouse embryos, but there are also important differences, which mean that animal embryos can not be used to model everything. Human eggs are much more sensitive to cooling than mouse eggs; a fall in temperature below 37°C irreversibly disrupts microtubules that hold the chromosomes together in human eggs, but not in mouse eggs.

Development of Contraceptives

Experiments are also underway to optimise conditions thought to be necessary for correct implantation. This involves studying the methods the mother's body uses to recognise the embryo before it becomes implanted in the wall of the uterus. Human embryos can be used in the study of contraceptive methods. There are various attempts underway to develop a contraceptive vaccine, to work either at preventing fertilisation of the ovum or implantation of the embryo. There are attempts to make gamete specific antibodies, but these need to be tested for the ability to block human in vitro fertilisation. To test some types there would need to be the production of early human embryos.

Clinical trials using a vaccine directed at a well-characterised product of the human embryo, human chorionic gonadotrophin, has begun (Jones et al. 1988). However, the abortifacient mechanism implicit in this approach makes it unacceptable to some. There has been a successful vaccine used in guinea pigs to make eggs infertile, so they can not be fertilised. This was done by producing antibodies against sperm in the female animals. This would be a more widely acceptable method of contraception, to those who view the embryo as protectable. It is found that 5% of women attending infertility clinics have antisperm antibodies, found in their vaginal secretions that reduce pregnancy rate (Aitken & Paterson

1989). The antibody prevents the binding of the sperm to the outside of the eggs, thus preventing fertilisation. This sort of contraception is irreversible if an inhibitor of the antibody is used. The actual molecules that are involved in this process on the sperm are yet to be characterised. Another area of research has been into the mechanism of action of existing methods of contraception. The intrauterine device (IUD) was thought to interfere with the implantation of the ovum, but is now thought to work by interfering with fertilisation itself (Barzelatto 1989).

The control of implantation and why genetically abnormal embryos are spontaneously aborted or fail to implant, is another area. There may be chimeras made with animals, or with genetically modified human embryonic stem cells, to study implantation. This is perhaps the logical extension of the preliminary research conducted on human embryos themselves. It will be important to define the developmental stage, such as cell number, which is the acceptable limit of these experiments, as the rate of development will vary.

How Much Human Embryo Experimentation is Ethical?

In Britain, the ethical factors and lack of legislation have led some scientists to delay the use of human embryos for experimentation. The British MRC (1982) and the Warnock Committee Report (HMG 1984), recommended bans on the experimentation on human embryos of 14 days age or over. This has recently become statutory in Britain. However, Britain has been one of the few countries to support any embryo experimentation. Some of the stated goals of this research have just been described.

The answer to the question how much experimentation is ethical, could be none, or some depending on the age and the experiment in question, or it could be any up to a certain age. One moral assumption that can be made is that it is completely unacceptable to make use of a child or an adult as the subject of a research procedure which may cause harm or death (Warnock 1985). The argument whether an early embryo is of the same status as a fully developed fetus is a slippery slope argument (Williams 1986), and was discussed previously in this chapter.

The pursuit of knowledge itself is not sufficient aim to justify ethically borderline experiments, there has to be a clear medical reason. The research aims are directed at the care of future individuals. There are many "gray areas", the intention of the research, and the primary effects or consequences that it may reasonably be expected to have upon the moral matters are necessary to identify. Many of a wide range of beliefs insist on no research (Chargaff 1987), while a few who believe the embryo has no rights have no ethical qualms about research. There is an intermediate view that human embryos should be respected, but those in the early stages of growth are not so protected that we can not study and learn from them (Edwards 1989). This view means that a human embryo is not equivalent to a mouse embryo, and so not open to any type of research.

A question is whether "spare" embryos created by use of IVF are different to those specifically created. In many European countries, research is only permitted on surplus embryos from clinical IVF treatment. The motive behind the origin may be different, and with the creation of "spare" embryos the original intent is not their death, but death is a consequence now that the donor has had a successful pregnancy and no longer requires more embryos to be implanted. The motive of those creating the embryos for experimentation is beneficial for future patients but

means death to the embryos under experimentation. For human persons, the good of an individual comes before the good of a species, and they may not be the same. The doctor is concerned with the individual, while the scientist may be concerned more with the species. In the case of a preembryo, it may however be justified.

Experimentation on human beings carries more moral requirements than for than on animals. If we believe we are justified in exploiting animals for the cause of human betterment the question of using live embryos depends on whether they have a higher moral status. This depends on the status we place on humans as a species. Singer (1990) would argue that beings that feel pain are higher in status than nonsentient beings, such as preembryos. Under that view, we would be able to do embryo experiments, but for the same trial, we might not be able to justify animal experiments. However, many people place higher status on the human preembryo than many animals, for extrinsic reasons. As discussed in the previous section the early embryo even if not yet a human "person", has the promise to be one. Is the sacrifice of such promise justified in the interests of other human beings? However, what if the alternative is to be dumped in the rubbish, as in the case of surplus embryos from IVF, or surplus gametes from normal human life? If we use preembryos it should be only when it yields a necessary contribution to clinical problems, with a reasonable chance of contributing to the well being of other individuals. Some theologians such as Karl Rahner would support embryo experimentation but not IVF, because the early experimentation is on an embryo not a person. There would be more concern for the birth of children after the involvement of third party gametes. However, others are against research itself (Walters 1979).

The early studies had limited supplies of embryos, but now human embryos can be made from the many eggs and unlimited semen is obtainable in storage banks. In the U.K., where embryo research is widely permitted, the shortage of human oocytes for research has led sterilisation clinics to consider offering inducements for those woman who will give their eggs to the clinic for research. The Interim Licensing Authority (ILA 1990), and some members of ethics committees are, not surprisingly, against any inducements. Though it is possible that a woman who did agree to donation would be put on top of the National Health queue for sterilisations. The ILA recommends that the only kind of acceptable inducement is a free operation, which could mean moving the woman to a private hospital to perform the operation immediately. It is certainly a contrast to many countries which only permit experiments on surplus embryos from IVF procedures, instead they appear to be trying to obtain as many eggs as possible (sperm are in abundant supply).

One means of regulation is the expressed need for all experiments on human gametes and embryos to be only done if consent of the donors is obtained, but more control is needed. It is very difficult to justify the use of inducement, of whatever kind, to obtain gametes for embryo experimentation. It is difficult to be precise about what type of scientific research each egg and embryo is to be used for, and once it has been donated to scientific research, even if for the solving of a particular problem, it depends on the scientist how they are exactly used. The alternative is very strictly controlled research, which is the situation in some countries, such as the Australian state of Victoria.

In contrast to putative gene therapy where the experimentation is to aid

specific individuals, in embryo research the experiment is intended to benefit the species, with the sacrifice of the embryo(s) involved. There is a distinction between research which is therapeutic, undertaken for the immediate best interests of the subject, and experimentation which has no immediate benefit as it is directed at broader putative long-term benefits. The long term benefit can be to embryos in general, or to medicine in general. Therapeutic experimentation has fewer ethical difficulties than non-therapeutic in cases where consent is not possible. The experimental treatment contemplated carries with it an element of ignorance as to the outcome, and should only be undertaken in the best interests of the patient when it is clear that more established forms of treatment are unsuitable. For therapy on embryos the symptoms treated could be before, though usually after, birth. The benefits hoped for and risks involved must be taken into account. The current situation is that no embryo that has been involved in an experiment should be replanted into a woman. When it is used, the genetic manipulation of embryos would require very delicate clinical judgement.

Embryo biopsy could be argued to be of importance to the future child, but not necessarily to that particular embryo. In many cases the embryo will be implanted after a good result, when in the absence of the technique its conception may not have occured. It is most important to the future child, that the embryo implanted was genetically normal, and free of disease, if the alternative is a serious genetic disease. This is a relatively new philosophical concept, but to many would be the common sense use of modern technology. In the modern family with few children, the future child's interests and parents interests are best served using this. However, we must carefully decide where to draw the line.

The major type of experiment generally considered are sacrificial experiments, the motive being to aid others. The decision on the grounds of motive is difficult. On the purely existential argument any embryos are of similar status. A human experiment must be moral in its inception, not just when it is done (Ramsey 1985).

In the arguments used to support the need for regulations on embryo research, a common objection is to the creation of human/animal hybrids. As stated above, there are some experimental reasons for creating interspecies hybrids as a result of interspecies fertilisation tests. However, some people use images of living animal/human hybrids to insight emotional objection to this type of research. However, most hybrids would fail to divide even at the initial stages of embryo development, let alone ever implant. While it may be a necessary precaution to prohibit such research if it involves later stages of development, if we support human embryo experimentation up to 14 days then we should also support animal/human hybrid research up to the same developmental stage, the implantation stage. However, only if the research is judged to be worthwhile and is subject to a controlling committee's consideration and approval.

Regulations are Required

What is imperative is that some guidelines be established in all countries involved in embryo experimentation (Edwards 1989). The most important regulation is the time limit for the *in vitro* growth of human embryos. The situation varies between European countries, all experiments are banned in Norway, and in West Germany. The West German Parliament is considering a law which would ban human gene insertion into germ cells, any destructive research on human embryos,

the formation of human hybrids or chimeras with other species, and the freezing of human embryos for IVF itself. It defines an embryo as a fertilised developing human egg from the time of union of the genetic material of the gametes, and also any totipotential cell which is able to divide and develop into an individual. The Bill prohibits clinicians allowing sperm to penetrate an egg other than for the purposes of producing a pregnancy. The main reasons for the harsh laws is the spectre of Nazism. It restricts IVF to married couples, and all embryos must be immediately implanted. While this eliminates the problem of surplus embryos, it may be medically unwise. It is a partway law, which is designed to allow IVF in a country where popular opinion is against embryo research. Any scientist guilty of embryo research may be imprisoned for up to five years!

A similar moratorium is in force in Denmark, which states that any surplus embryo must be immediately destroyed, and no cryopreservation is permitted. There has been a recommendation by the Danish National Research Council that a one year limit be imposed on freezing, and that it be used, but it is unsure if this will be accepted (Gunning 1990). After the Vatican (1987) instruction against "artificial procreation", the Catholic Universities in Belgium decided not to undertake embryo research. However, at Leuven they have introduced cryopreservation for surplus embryos. Research is permitted at private clinics, and there are no formal committees, because in Belgium abortion was illegal until April 1990, and this debate has taken attention away from embryo experiments.

France was announced it would introduce the Life Sciences and Human Rights Bill in 1989. This law would forbid any attempt to maintain an embryo in vitro beyond 7 days, unless the National Bioethics Committee consented to a 14 day time limit. However, it has been stalled for a year after adverse public debate, and a substantial minority of the committee want a total ban on embryo research. Fears of eugenics, rather than embryo rights, underlie this (Hughes 1990). From 1986 until 1989 no research on preimplantation diagnosis was permitted, but there is research permitted up until 7 days in relation to the methodology of IVF. Only surplus embryos are used.

In Holland there is a moratorium on the creation of embryos for research, but research on surplus embryos is permitted with the written consent of the donors. It is likely that legislation will allow research up to 14 days, but there is currently no embryo research. Research on "nonviable" surplus embryos up to 14 days is permitted in Spain, but the creation of embryos for research is forbidden (as is research involving cloning, parthenogenesis or genetic manipulation). Research is permitted on surplus embryos only in Sweden also, up to 14 days, and after consent of the donors.

The recommendation of the English Medical Research Council, British Medical Association and Royal College of Physicians is that human embryos should not be cultured in vitro beyond the implantation stage, for any purpose. This was the age limit recommended by the Warnock Committee (HMG 1984) and the earlier Government White Paper (HMG 1986). It finally became law in the U.K. in 1990 after a controversial Human Fertilisation and Embryology Bill (HMG 1990). During the voting, the bill had two alternatives in the section on human embryo research, either no research, or authorised research up to 14 days after fertilisation.

The U.K. Bill received much support from the members of the House of Lords. They supported research on human embryos up to fourteen days after

fertilisation, by a votes of 234 to 34, and 214 to 80, at different readings. The House of Commons voted in favour of the principle of experiments on human embryos up until 14 days, by 364 to 193. The law allows for the use of deliberately created human embryos for research, which is the source of 75% of embryos currently used in the U.K. The Bill does not place restrictions on the criteria for treatment, except that all research and IVF treatment must be at licensed clinics.

There may soon be some European legislation. There have been two Council of Europe recommendations (Nos. 1046 (1986) and 1100 (1989)) on the use of human embryos. They want to give legal protection to the human embryo from fertilisation, and to decide on limits for experimentation and to try to prevent some countries becoming liberal havens for embryo research, but the situation remains variable.

The situation in Australia is under some legislation, but is still developing. The limit in the state of Victoria is determined by their Infertility (Medical Procedures) Amendments Act 1987. The Act allows for approval of research by a Standing Review Advisory Committee on embryos surplus to requirements, up to 14 days. It prohibits research involving cloning or cross fertilisation of human and animal gametes. It allows research on the process of fertilisation before syngamy (defined as the alignment of the mitotic spindle of the chromosomes derived from the pronuclei), about 22 hours, on eggs not destined to be replaced. There has been confusion on the distinction between the research use of specifically fertilised eggs up to syngamy and the possibility of using surplus embryos from IVF for research up to 14 days. The Victorian government had given powers to this Committee, but when they approved an experiment for after 22 hours, the government overruled them, the experiment was one of embryo biopsy of slow growing embryos. This lead to a moratorium on an embryo biopsy project and other research. In South Australia only nondetrimental embryo research is allowed up to 14 days. In New South Wales the limit may be 14 days, if the New South Wales Law Reform Commission recommendations are adopted. In New Zealand there is no law applying to an embryo prior to implantation, the preembryo has no legal status. However, there are only 3-4 clinics in New Zealand, so little research is possible.

In the USA there was a defacto ban on federal funding of embryo research since 1975 as approval from the Ethics Advisory Board is required. This Board is still to be established, because attempts to balance members who support abortion with those who oppose it have failed. It should be an embarrassment to American politics that quarrelling about the abortion views of members has delayed its approval. It suggests that members will automatically support one side or the other without functioning as a real ethics committee, in advising on individual cases. In 25 states there are statute restrictions on fetal experiments. In other states the federal limit of 14 days may be used. The criteria taken into account include the purposes of the research, the effect of the research on the embryo, whether it is *in vitro* or *in utero,* the stage of development, and the relationship to abortion. Research on *ex utero* embryos is allowed if therapeutic to the embryo, and nontherapeutic research is allowed in thirty states before viability (Andrews 1988). In most states early embryo experimentation is legally possible in facilities not receiving federal funds.

In Canada there is no legislation to control research. There are MRC Guidelines for projects using funding from the MRC. They approve of research if there is no other organism available, the research is considered worthwhile, and up

until 14-17 days of development. They do not approve of the creation of embryos specifically for research. The Law Reform Commission of Canada has recommended that all non-therapeutic embryo research should require the approval of an ethics committee. It suggested a limit of 14 days, and that the embryos should not be implanted, and no embryos should be specifically created for research. It recommended the forbidding of research involving cloning, parthenogenesis and cross-species fertilisation. There is a Royal Commission established, which is expected to report in 1991.

The recommendation of a 14-day limit is seen by some as arbitrary, and the time limit could be increased as embryos are able to be kept alive longer. However, as discussed, there are some strong grounds for making 14 days a cut off limit. The limit that some see for scientific research to be associated with is the possibility of nervous coordination, between day 12, when the first neural tissues begin to differentiate, and day 30 (see earlier), when the sense organs begin to develop (Edwards 1989). Some say that it is preferable not to define an exact point, but to relate the nature of studies undertaken between these two periods to the clinical value the work is expected to yield. The Helsinki Statement on human IVF recommends the 25 day limit on growth of embryos. So a better alternative to the 14-day rule would be to establish a powerful ethical committee which demands justification for every piece of research. The 14-day rule is too generous for some types of research, for example, the study of chromosomes can be largely done at day 5, whereas studies on the differentiation of the hemopoietic system would require embryos at day 14 or later, and for some studies, such as those on the myocardium it would need growth until day 20. The arbitrary line required differs. The price to pay for no research on embryos includes a longer continuation of the suffering caused by genetic disorders, and greater risk to mothers using IVF. The committee would have to be scientifically trained so that it could make judgements on whether the research in question could be done on animals. There have been results of some human embryo experiments published which cover research not yet done on animals. Although there are some differences between animals and humans, the preliminary work should be done on animals, then the experiments considered for using human embryos.

However, even if there are many benefits, it would still not be justified if the research is unacceptable ethically. From the results of the discussion on the status of the embryo, my view is that a time limit around 14 days is ethical. The 14 day time is morally safe if the motive of the research is good and the embryos are only used when all possible animal work has been completed, i.e. they are treated with high respect. If we permit IVF treatment, than we should allow research that is needed to improve that treatment. The concept of regulated use of science is not new. Research is not sacrosanct, and there are many areas where researchers are regulated by moral laws, such as in the use of animals, human beings, or of dangerous pathogens. There are many areas which are regulated but do not have an outright ban, so there are reasons to believe regulated research would work. It may be difficult to prevent a time limit for growth of human embryos being exceeded, but if researchers know that they would be imprisoned if they publish results which other scientists would know had been obtained by use of illegal material, this should be a strong enough deterrent. An alternative seen by some researchers is the generation of a tissue culture cell line which has the attributes of a stem cell, i.e.

many other cell types could be differentiated from it. Research to obtain such an embryonic cell line is intense. The guidelines will have to include the prohibition of growing an embryo older than the 14 day *in vivo* equivalent, probably measured by the formation of the primitive streak, from any type of cell line or embryo source.

The cutoff point is arbitrary, and different governments have made different decisions. I support the 14-day age limit for growth of human embryos *in vitro*, and it is also important that no experimented embryos are replanted until safety can be ensured. Modern embryology does indicate that until an embryo is implanted, and has passed the stage of twinning or recombination, and is clearly an ontological individual, it is of lower status than a biologically stable embryo. In exceptional circumstances which will lead to very important clinical results the established committee should have the powers to grant embryo research licence, for an age limit up to 14 days, as seen necessary from the research to be conducted. The embryos could be used from those which are frozen "spares" from IVF, or those specially created, as the status is the same, but their creation should be regulated. The determination of the number of embryos required will depend on informed scientists being present on the committee, however they should be balanced by nonscientists. The embryos are given a very respected status, but are available when necessary.

The next major step in embryo status must be when the neural tissue is beginning to function, this includes two stages, the feeling of pain and the formation of the cerebral cortex. The idea of brain life is important. Because of the doubts regarding embryo status between 14 days and such a time it is reasonable not to grow embryos past 14 days age. However, it is still consistent to consider an age for selective abortion past that time *in vivo*. There is sufficient difference between growing an embryo *in vitro* specifically for experimentation, and the killing of an embryo after that time in certain circumstances when *in vivo*. However, the limit to that killing could be placed at 6-8 weeks, the beginning of the formation of the cerebral cortex.

Brain Grafts from Aborted Fetuses

Although this is not a genetic or reproductive technology in the narrow sense, because it is a very topical related issue I will briefly consider it. We need to see how how the ethical principles would begin to deal with this issue, because this area of fetal research may result in the use of more human embryos than experiments at the early stage. The prospect of therapeutically effective fetal tissue transplants for diabetes or Parkinson's disease has made people examine older questions about the use of tissue from aborted fetuses. The demand may greatly increase if these treatments are effective, therefore the scale is much greater than the limited experiments previously performed. Fetal tissue from aborted fetuses have been used for many years, and it shares some similarities to the use of surplus IVF embryos in research, except that fetal material must be from a dead fetus. Dead fetuses from induced abortions have been sold and used for research. The opponent of abortion will object to the action of obtaining tissue, but it is argued that it is impracticable for people not to profit from the knowledge that has been obtained. At least the result of some research has led to clinically valued knowledge, from what otherwise could have been seen as a tragic waste of life.

There have been some important scientific and medical contributions from past fetal research. Prenatal diagnosis has been developed which has benefits in reducing the proportion of babies born that are handicapped or suffer from genetic disease. Research is needed on the development of new techniques to extend the range of diseases and to develop earlier testing procedures. Fetal research has been used to develop fetal tissue culture cells which have been used in vaccine development. They are also used in the development of *in utero* surgical therapies, and the assessment of risk factors and toxicity levels in drug production (Hansen & Sladek 1989).

Perhaps more importantly, there is quite a poor record for successful fetal tissue transplantation, one factor is that multiple donors are often necessary as tissues from a fetus are much smaller than the child or adult (McCullagh 1987). However, there are several advantages that make fetal tissue useful in transplants; it grows rapidly, it is very adaptable, and when transplanted properly it evokes little or no immune response in the host (Greely et al. 1989). There is a shortage of small organs that are needed for transplantation into children. During the last two years there has been growing attention on the question of brain cell transplantation, from aborted dead fetuses to adults suffering from neural diseases such as Parkinson's disease. Despite the initial encouraging results saying that the recipients had improved after the transplants (Hitchcock et al. 1988, Madrazo et al. 1988), by mid 1989 and after 350 human tissue transplants in several countries, there were many less positive results. There have also been many adrenal tissue transplants into adult brain, with less success. Often the recipients are already very sick, and one may expect more success in patients in earlier stages of their illnesses. There is uncertainty at present on how they work in the few cases where there is some improvement. At the time of writing in 1990, the only very promising evidence comes from detailed scrutiny of isolated cases . The first very successful case of the recovery from Parkinson's disease symptoms came from a Swedish team, who used fetal implants from several 8-9 week fetuses (Lindvall et al. 1990). The patient regained movement following the transplant, but the long term effects are unknown. The transplanted neurons had increased levels of dopamine, an important neurohormone that is at abnormally low levels in Parkinson's patients. Other successes have been in increasing the amount of time that patients are able to control movements in response to drug treatment.

Animal experiments indicate that fetal brain is better than adrenal tissue, but there are also doubts on these studies, in which animals are given similar symptoms by drug treatment, prior to transplants rather than the longterm progressive neural decay of human adult patients. In those cases with improvement, the transplanted cells themselves seem to die, but they may stimulate dopamine production in surrounding cells. The mechanism is unknown. There are signs that alternatives may emerge, with the discovery that Deprenyl, a monoamine oxidase inhibitor, substantially slows the rate of neurodegeneration in Parkinsonian patients (Tetrud & Langston 1989). There is also hope that neural transplants may aid people with spinal cord injuries, allowing the spinal cord to rejoin at a break.

As I previously mentioned there are many experiments which could be done on human embryos which will provide results of benefit to others, but regard the embryo as expendable. Several aborted fetus of 18-20 weeks gestation, have been kept alive for a few hours in experiments to try to develop an artificial placenta.

This type of experiment can be argued to be unethical because such a developed fetus should not be aborted as it has neural activity. However, if the experiment is independent of the abortion, should such an experiment be used, when there is no chance of survival? When passing legislation this type of research should also be considered, and flexibility maintained, by giving powers to an ethics committee to decide on cases which may arise that are not considered in the law. The protagonists of the use of human embryos for experimental purposes argue that the best species for experimentation to help humans is man, as to pass from preliminary animal studies to human trials is a move which has unknown risks, no matter how successful the animal trials are. They argue that we should not waste this opportunity to use human fetal tissue to benefit humanity. Before this new experimental subject became available in great numbers animal experimentation was used. We may not be able to justify research on an unconsenting research subject, even if there are consenting patients (though they are often sufferers of neurological disorders) already in existence and in serious need of radical treatment. However, most would judge that a discarded nonviable embryo or fetus is lower in status than a person suffering from severe disorders, and consider that the principle of the idea is ethical.

A disturbing possibility is deliberate pregnancy to obtain spare parts for a child or adult requiring an organ donor. There have already been over half a dozen cases in the United States of this being reported to provide an organ donor for a sick child in the family. One such case was reported by Clark et al. (1989) for parents who wanted prenatal diagnosis to be carried out to determine whether the fetus would be a compatible bone marrow donor for their first child who required bone marrow transplantation. In this case if the fetus was compatible they would bear the new child as a bone marrow donor after birth. The clinic decided it would not do this screening as it was not concerning the individual fetus and they do not think prenatal diagnosis should be used to benefit a third party or to facilitate the conception or abortion of a fetus for the purpose of generating an organ for transplantation. However, people have still brought about the birth of babies as bone marrow donors for their sick siblings. Actually, if it is a genetic disease, the new fetus could suffer from the same disease and be a bad donor to choice. If we live in a society permitting abortion for minor social reasons, then the desire to provide an organ donor could be seen as a better motivation for an abortion. However, it would begin a trend to viewing babies as consumer materials, which most people view as wrong. Despite the possible worthy motivation in individual cases, the trend should be stopped, as for sex selection. Some philosophers believe that there is nothing wrong with more abortions, especially if done for a "good" reason, but there is a significant, and in my view major, difference between tolerating, what is in terms of motive, an accidental abortion and allowing deliberate pregnancy for abortion.

Even if the treatment can be made to work, there will still be ethical problems. The numbers involved at present of suitable aged abortions is sufficient, however as the age for abortion becomes younger, and if the hope of many that abortion becomes much rarer in the future, is realised than there will be a shortage. The research should develop an alternative, such as some sort of neuronal stem cell line, which would be ethically more acceptable to all. If this sort of use of fetuses is going to be ethical the decision regarding the abortion and the transplantation must

be keep separate, there should not be any motivation for the abortion in the woman's mind. The key concern for most people is that the two procedures need to be isolated. That is possible at the level of a hospital. In Britain the Royal Commission chaired by John Polkinghorne (HMG 1989a) has supported the use of fetal tissue transplants, as long as there is no direct contact between the abortion clinic and the research institutes. The Australian National Health and Medical Research Council guidelines allow the use of separated previable fetuses (20 weeks or less than 400g weight) or fetal tissue for approved research or therapy. The abortion procedure must be completely separate. A similar ruling applies in France for the guidelines, however the French National Ethics Committee does not support fetal transplants for Parkinson's disease treatment because of a lack of proven therapeutic value (Gunning 1990), but this may change with positive results.

Fetal research is permitted in the USA, but no federal funding has been given since March 1988 for projects involving transplants to humans. A Human Fetal Research Panel reported in December 1988 supporting therapeutic transplantation of human fetal tissue, as long as abortion is permitted by society and the use of the fetus is subject to informed consent of the mother. However, these guidelines are yet to be approved, and the moratorium on research using federal money was reimposed by the current U.S. Administration. There is research performed in private institutions. Eight states (Arkansas, Arizona, Illinois, Indiana, Ohio, Lousiana, New Mexico and Oklahoma) have laws prohibiting the experimental use of aborted fetal tissue obtained from induced abortion. The Uniform Anatomical Gift Act allows the donation of fetal tissue in every state provided there is documented parental consent (Gunning 1990). There is still federal funding of some projects involving transplantation of human fetal material into animals, for example for use in the study of the human immune system in mice.

Certainly, a prior requisite of any ethical use of fetal tissue is the separation of the abortion decision and later use. These concerns demand the prohibition of the donation of fetal tissue to designated recipients, the sale of such tissue, and the request for consent to use the tissue for transplantation from the mother must be asked for after a final decision to abort the fetus has been made (WMA 1989). It also means that the decisions regarding the technique used to induce abortion, as well as the timing of abortion, are based on concern for the pregnant woman, not in providing a fetus for transplant use.

In the USA many abortion clinics are privately operated as businesses. If the businesses can sell fetal organs, they could lower costs of abortions and be more competitive, while also being available to poorer people. There are many arguments that discourage the commercial exchanges of human tissue, and given the strong feelings aroused by abortion itself, commercialisation would not be generally acceptable. It is better to base social policy upon altruism, than on commercialisation. To use fetal tissue that is specifically aborted for that purpose is to treat the fetus as nothing but a medical product and the uterus as a factory (Greely et al. 1989). It demeans the potential humanity of the fetus. The possibility of the fetus being used could become a redeeming feature in the minds of women, and this would be almost impossible to eliminate if wider therapeutic use arises.

If society accepts abortion, at least up to the time of 12 weeks, as many countries do, then it would be double standards not to allow the controlled use of the aborted fetal material. The most important people who are the subject of this

research are not the fetus, or the mother, but the recipient of the transplants. This is not the way that this issue is often presented to the public, but this only illustrates how preoccupation with one issue may cloud our sight from the more important ethical questions.

The fetal brain cells must be alive, which raises the question of determining death, usually the criteria of nonviability is substituted for actual complete brain death. The optimal age for neural tissue donation of aborted fetuses is now thought to be 9-10 weeks, but may change as experience is gathered (Jones 1989). One of the key requirements is that the cells can regenerate, and the best time to take cells is just after they have had a cell division. This limits the window to 8-12 weeks, the best balance of the amount of tissue and the regenerative capacity.

There will always be ethical problems in using fetal tissue at any age beyond which the individual is thought to develop, that varies with people. However, if we have decided on that age then we will strive to have abortions occuring before that time no matter what the uses of the fetuses. While those fetuses may be available as donors now, we should strive to bring the age back, which will lead to the situation where they are not available. There should be alternatives developed in the short term, so it will not be a long term dilemma. The time limit we may be aiming for is 8 weeks.

It will be impossible to satisfy the variety of strongly held views on what time limit, if any, is acceptable for human embryo experimentation. We should work to a society which maintains a high respect for human lfe, at the same time recognising the dilemmas faced. We can be certain that the fetus begins to feel pain at some stage after 8 weeks of development. We can also be certain that the fetus is not self-aware until later than this, perhaps around 20 weeks. Viability is possible at 22 -24 weeks. These stages represent major increases in the moral status, and we should recognise these points in our attitude to ethical questions involving the human embryo. They should be represented in the law, as we protect against other types of human experimentation or abuse. Recognition of these points does not mean we can do anything we like before these times, what the different stages of development present us with, is a hierachical system of the increasing moral status of the human embryo.

6. Animal Rights

Making New Strains of Animal

Historically, mankind has developed new breeds of animals displaying specific characteristics. Most of these animals have been for agricultural use, but recently many have been made for biomedical research. Genetically engineered animals are becoming the preferred source of experimental animals. The growing number of transgenic animals described in recent scientific papers, serve to illustrate the rapid developments. Scientists prefer to use standardised animal strains for experiments, and in the pursuit of knowledge they want to study the affects of genes on whole animals. Only by studying the complex animal systems will the effects of altering the genes be seen in transgenic animals, and be understood. Many mice strains have been used for several decades in laboratory experiments, so the concept itself is not novel. New strains of animals that are diseased, and feel more pain, have been developed and the question has to be asked, whether it is right to breed them.

New strains of mice, such as those deficient in the enzyme HPRT (Hopper et al. 1987, Kuehn et al. 1987), have been made, when these embryonic stem (ES) cells introduced to the embryo enter the germline of the animal (see chapter 7). Recently, a new method which can potentially select ES cells with any new genetic manipulation has been developed, so that any isolated gene could be inserted (Mansour et al. 1988). Many mutations have been made in different genes, and the results can be seen in the resulting diseased animals (Capecchi 1989). Many mutations can be tested simultaneously, up to 20-50 retroviral vectors per cell can be introduced into ES cells and used to create germline chimeric animals. Most work has been done in mice (Jackson 1988). Evans and Foster presented the results of 57 different insertions in July 1988, and more are continually being made (Evans & Foster 1988). New mice such as the first female mouse with XY sex chromosomes have been reported. These mice were made after they set up genetic screening affecting sex determination. Each mouse was mosaic in the germline for ES cell derivatives and up to four independently segregating patterns of retroviral insertion were seen. With the average copy number of 12 retroviral vectors used per ES cell, it is theoretically possible to screen for 48 insertions per chimaera made (Lowell-Badge & Robertson 1988). This has resulted in the generation of new strains of animals.

Animals can be made as experimental models of human disease. For example, the first mice strains that are deficient in an enzyme HPRT were made as potential animal models for the human disease Lesch-Nyhan syndrome (a rare disease, in

which the sufferers start to eat their own flesh). Another example is the insertion of a human gene for apolipoprotein CIII in mice, as a model of the human disease hypertriglyceridemia (Ito et al. 1990). This condition is common in people with premature coronary heart disease, and making a mouse model will be useful for learning more about the role of this gene in that. Other animals have been made to study the effects of different possible cancer-forming genes and genes involved in development, and they do have many benefits for medical research.

Drugs for use against AIDS are being tested in mice with a human immune system. The mice were bred with a deficiency called "severe combined immune deficiency" and are abbreviated SCID-hu mice (the "hu" stands for human tissue). SCID-mice are being used for testing the effects of different gene insertions (Bosma et al. 1989). The mice strain is genetically devoid of any immune defences, so when human tissue (usually the thymus tissue which contains immune cells) is implanted the mice respond as if human. Researchers are using these mice as living laboratories to study how the AIDS virus affects the human immune system. This may sound extreme, but considering that the only other animal model for AIDS is a chimpanzee, it is preferable at least to that option.

The ethics of some of this work is challenging in the context of making very unusual and often diseased animals, though medical researchers justify this on the application of the research to untreatable human diseases. These problems are not new in themselves, but the rapidity of change and the types of changes that are possible make it essential to look at the possibilities. With the techniques used for fusing of blastomeres, egg cells and ES cell lines, it may soon be possible to make clones from these cell lines via cell fusion. Eventually one can envisage the development of not just an ES cell line but an independent blastomeric one. There are ES cell lines for mice, hamster (Capecchi 1989), sheep, pigs and work on ES cell lines for other animals is well advanced. Chimeric sheep, goats and cattle have been born. There are teratocarcinoma-derived cell lines for humans (Engstrom et al. 1985, Graham et al. 1987), and unproven ES cell lines for humans (to prove that they are real ES cell lines requires their use in making chimeric animals).

As we have gathered from some of the examples of animals altered by genetic engineering, there are major changes possible in animal characteristics and even category. Conventional animal breeding dramatically illustrates the variety of dogs that we have accepted. There is a great deal of difference between the largest and the smallest dogs, and between different breeds of cattle or horses. Nature itself is full of variety, and the selection of different characteristics in domestic animals has relied on this variety. There has been increasing use of the new technology to increase agricultural production by undertaking such things as altering genes in breeding, or altering the environment as in battery farming. However, there is a point beyond which it is unethical to use animals as a means to an end.

The goals of genetic manipulation must be carefully chosen. Both increased productivity and concerns about animal welfare will remain the most important factors. The size of food animals may be able to be controlled, and rapid growth and maturation are qualities that may be desired for economy of production. Other animals are being designed to become faster growing, or have other characteristics that may increase financial returns, such as disease resistance. The ethical concerns vary with the genes desired, and many people accept the use of gene transfer by conventional animal breeding. If disease resistance is conferred this might be seen as

desirable. But what about the alteration of animals growth rates? If a gene can be inserted so that animals do not feel pain from experimental use, should this be done, so researchers can use those animals in experiments? Or is it unethical to alter such fundamental feelings, as pain, which is of physiological value to animals? The boundary to the genetic manipulations used on farm animals is going to be difficult to decide, and may be different in different cultures.

Ethical Limits of Animal Use

The animal welfare movement of modern times was lead by Christians during the last century, especially in Britain, but during the last two decades there have been extremists which have led the public campaigns and have even began terrorist activities (Philp 1990). We all should be concerned about animal welfare and be involved if we see abuse, but in perspective to other problems. There are a variety of ways of looking at animals, it is important to compare them briefly. We must examine the status of animals in light of what we can reason about them, this includes any new scientific knowledge which may elevate the status of animals. Recent biological knowledge has shown that higher animals can exercise free choice and some can learn to count (McGonigle 1985), and this should change the way we regard them (Gaffney 1986). It means that if we do use them we treat them with more respect, not just pity, but mature compassion (Bowker 1986).

Secular philosophers have had to concentrate on different ways of claiming animal rights. They say that since all life evolved, the chief division of life is between plants and animals, man is only one of the animals. Other animals should possess equal rights to humans as they are part of the same class. However, it is clear if you examine animals that there are many types.

Another approach has been to look for characteristics that have been claimed to make humans higher than animals. As we learn more of animals we can critically examine these characteristics, and it is clear that animals have been found that share many of these with humans. I talk of human as a species, rather than as individuals, on the criteria that all humans are of equal value. If we use this approach then we would give animals potentially the same rights if they have equal capacity for the characteristic chosen. Intelligence and intellect can be distinguished, in the sense that intelligence is a relative quality. Language ability is one sign of intellect, but it is very difficult to estimate the language ability of animals who use very different methods. One way is to examine the complexity of the language, which would eliminate most animals from being close to humans, but there would still be doubts over some. It has been found that chimpanzees can be taught sign language, and talk to humans in it, but only to the extent of composing two or three sentence replies. This represents a stage equivalent to a human baby learning to talk, before they can start to actually make longer sentences. Chimpanzees have not composed long sentences, but their must still remain enough doubt about their ability to give them certain rights.

It could be argued that there is sufficient intelligence shown by them to prevent their use by humans, and that would be consistent with what we know of their brain structure, behaviour, and the doubts on early views that placed them with "lower" animals, certainly more consistent than the widespread use of chimpanzees,

gorillas, orangutans and other higher primates in scientific research. Though during the last few years, with added pressure due to the possibility of extinction of these animals, there has been much less research use of them. Dolphins are another species whose intelligence and rationality is sufficient to protect them from use in destructive research. There status is sufficiently high to prevent their destructive use, though their is still a case for behavioural research to try to understand them if it is well controlled and humane. Their behaviour is beyond that of reflex behaviour or the unthinking genetic level of response seen in lower animals. In a following section we will consider the major argument used by utilitarians against animal research, that of promoting pleasure and avoiding pain.

Another of the major criteria has been the universal human possession of a uniquely moral will and the autonomy inherent in this. Animals lack this capacity for free moral judgement, and if they are incapable of exercising, or responding, to moral claims then they do not possess the same sort of rights as humans do. We can talk of humans as a species, rather then talking of the few exceptions who do exhibit this characteristic. We still have duties to animals, but not the same that we owe to humans. The grounds of our duties are not based on giving them equal value to humans and the corresponding rights, but they are of lower valuation. If we owe them certain duties we can say that they possess certain rights in the same way that we use the word "rights" to speak of the duties we owe other beings.

Religious Views of Animal Status

The motive behind the use of animals alters the morality of their use in some religions and in some philosophical systems. Animal sacrifice for worship is used in Islam, but they would generally condemn scientific research or battery farming. Vivisection is allowed under circumstances where there is no pain or disfigurement and if other animals benefit. The use of animals in science is under the same moral codes as applied to humans. Even though the animals possess a lower consciousness, Islam says animals know their own mode of prayer and psalm, a voluntary act of praise (Masri 1986). The killing of any breathing beings, except for food or religious sacrifice, is high on the list of deadly sins. Hindus, Jains and Buddhists believe that we will be reborn as another living animal, which creates their bond of caring and compassion for animals (Bowker 1986). So they will reject animal sacrifice, even though the sacrifice of an animal won't kill what is essential, in the reality, the soul, of that animal.

Like other religions, Christianity agrees that the scriptures and traditions may not have so much as a concept of animal rights, but that animals do have valid claims upon us. It is an issue of human responsibility which we cannot ignore. Different religions have different accounts of what constitutes animal nature. Animals cannot be viewed simply as expendable raw materials for our designs (Linzey 1986), they do not exist simply to serve us, the doctrine of creation is opposed to anthropocentric notions.

The Bible often mentions animals, as Israel was an agricultural community. God owns everything of creation, including all our cattle (Ps. 50:10) and He cares for them all (Gen. 8:17, 9:4,10; Ex. 23:5; Deut. 12:23, 25:4; Num. 22:32; Prov. 12:10; Ps. 36:7, 104:10-11, 145:9,15-16, 147:9; Job 38:26-27,41; Jonah 4:11). God is not even careless of birds (Matt. 6:25, 10:29). God's mercies are over all His works (Ps. 145:9), and animals should also rest on the sabbath (Ex. 23:12;

Deut. 5:14), and should be fed first, before the farmer (Deut. 11:15; Num. 20:8). Animals can be eaten and farmed (Gen. 9:3; Deut. 12:20), as man has dominion over every living thing (Gen. 1:28), the fear of man being in the animals (Gen. 9:1-2). The use of animal sacrifices (Lev. 22:24) does not mean animals should be sacrificed for the selfish pursuits of man, the practise of animal sacrifice was to bring God into the focus of men's hearts in place of their own selfish desires, and was not necessary after the birth of Christ. We must respect animal life, some believe this is why that Jews could not eat flesh with its blood (Gen. 9:4), though that may have been more a recommendation applying to health in avoiding eating contaminated meat.

In the New Testament we see some of the verses of the Old Testament being used in an allegorical way, not directly applied. The two most important factors are respect for God's creation and love, which is the fulfilling of the law (Rom. 13:10). There is a certain unity of life which makes us respect animals. Early Christian theologians such as Aquinas regarded animals as irrational creatures that weren't directly possible of human friendships. However the loving concern to preserve irrational creatures may be both motivated by their utility to man and being of honour to God. The tradition of the Roman Catholic church is to regard animals as means to human ends, and the moral objections to cruelty on animals are more concerned with fear that those inflicting pain will contract habits of cruelty. Death is not the greatest evil that we can imagine, and there may be more important things in life than living by the easiest means. Christians should see things in terms of the Kingdom of God, and love applies to all creatures of the earth. The attitude of St. Francis, to talk of sister cows or brother dog, is a picture which we should not forget.

Speciesism is a word used to describe the view that man is the only species with protectable "rights" and that animals do not have any rights (Singer 1976). There have been several famous proponents of this view, a couple of the more fundamental were Aquinas and Descartes. The Bible has often been criticised by nonChristian animal welfarists because of its assertion that man is uniquely made in the image of God, has dominion over the rest of creation including the permission to kill and to eat animals. Most people are speciesists, and would not consider the claim that we should regard animals the same as humans as quite sensible and even obvious (Cohen 1986). There are many morally relevant differences between humans and animals. However, the belief that man is unique does not mean that animals have no rights, that we do not owe them duties. There are certainly ethical codes in most religions, though they are often not followed.

Philosophical Views of Animal Status

One of the most important criteria in judging the use of animals by humans is that of avoiding the infliction of pain. The Oxford Dictionary would define pain as "suffering or distress of body (from injury or disease) or mind." Philosophers have distinguished pain from "suffering." Bentham (1789) relies on a notion of animal suffering rather than just pain. Regan (1983) defines suffering as prolonged pain of a certain intensity, and argues that no individual can suffer who is incapable of experiencing pain. The capacity for suffering and/or enjoyment has been described as a prerequisite for having any interests (Singer 1976). Individuals can experience pain from suffering of the body or mind. This type of criteria is prevalent

in utilitarianism.

Judging pain is subjective, there are different categories of pain such as acute, periodic or chronic and the pain threshold varies between different beings, people, cultures and circumstances. There are no major biological reasons for the idea that human pain is intrinsically more intense than animal pain (Iggo 1983). There are parallels in the way animals and humans respond. Many of the neurotransmitters are similar between higher animals and humans. It is possible that animals do have a different quality of "pain", as the frontal region of the cerebral cortex of humans is thought to be involved in feelings of anxiety, apprehension and suffering components of pain. This region is much smaller in animals, and if it is surgically treated in humans it can make them indifferent to pain. There are differences seen in the types of pain receptors, some respond to mechanical stimuli, some to noxious heat or irritant chemicals, and some to severe cold. Studies in human fetuses have shown the early appearance of sensation before pain receptors in the skin are developed. In human fetuses the myelinated fibres develop much later than the nonmyelinated fibres, so it is possible they feel more pain at this stage, then they do later on, or when born (McCullagh 1987).

If we look at the boundary beyond which organisms feel pain, we could put the dead, depending on our criteria of death. We could probably put the unconscious, including those under general anaesthetic. We could say that beings under local anaesthetic may not feel physical pain, but could feel anxiety, as is felt if one being is watching another suffer pain or what appears to produce pain. This capacity is part of being sentient, the capacity of a being to perceive, or understand, what they can sense (see or hear or feel). Many of the motor reactions to noxious stimuli can occur in unconscious beings, some extending from the brain stem, including vocalisation.

We may all agree that animals can suffer, but the question is how much does it matter? There may be a choice between human welfare and the suffering of nonhuman animals. Many people accept that all humans are equal in moral status, and all humans are of superior moral status to nonhuman animals. From these two moral principles they put human welfare ahead of animal suffering. Peter Singer (1976) argues that these two moral principles cannot be defended within the terms of a nonreligious approach to ethics. He concludes that there is no rational ethical justification for always putting human suffering ahead of that of nonhuman animals. He argues that "if we are considering public policy in a pluralistic society, we should not take a particular religious outlook as the basis for our laws" (Singer 1990). While this is true, it does not imply that we need to take rational utilitarian philosophy as the basis for public policy either. Many different people's cultural and religious views are more consistent with human beings having a higher moral status than animals.

However, it is still important to summarise his argument, as it does have consequences for the way we regard animals, and we should improve their treatment. The problem with saying that humans are of higher moral status than animals is that while the human species may have higher mental capacities than animals, not all people do. The word speciesism reflects this view, which has its roots in the Judeo-Christian belief that humans are made in the image of God. However, in rational philosophy we cannot prove this. We should focus on the individual when considering ethics, which has been a focus of the movements

against sexual or racial discrimination also. He argues that we should consider all beings who can suffer in our moral considerations, regardless of species (Singer 1990). However, Singer would still not say that the deaths of animals are equal to the deaths of all humans, as there is an additional factor of the awareness of the future that humans have, which most animals do not have. To kill a human being destroys all the plans that they have made, a feature of humans. He also acknowledges the importance of extrinsic moral factors, such the feelings of family members if one dies (though this is shared with some other familial mammals). At the practical level, the feeling of pain is the first major guiding principle for animal treatment. The second is that we should not kill some animals, if they have self-awareness such as higher apes, and probably other animals such as dolphins. We do need to consider the findings of animal studies on the level of self-awareness that some may possess.

There are already many painless experiments performed on animals, and anaesthetics are often used if pain is involved (Frey 1983). Government regulations on animal use and experimentation emphasize the importance placed on avoidance of pain, and regulations limit the amount of animal suffering and experimentation. Many believe that there is a world of difference between experimentation that does and does not involve pain, including possible suffering through confinement in small cages (Sprigge 1983). There are some very efficient pain-killers, some of which can be used for long term pain. There are chemical nerve blocks which can be used to block pain from particular areas of the body for several months, or physical methods. Animals can be made to be like vegetables by removing the pain pathway. Animals may be perceived as feeling less pain, because of their rapid recovery rate from surgery, or the presence of what seem appalling injuries in some animals in the wild that apparently do not sense much pain. However, we do not know how much pain they feel.

While actively producing pain is seen as an evil, sensation of pain is necessary as pain is important in the proper functioning of nervous systems, so feeling pain should not be seen as evil. What is seen as an evil is the production of pain in other beings, or the introduction of disease into other beings. Because pain is a basic sensation we may object to manipulating it permanently out of strains of animals, but what argument would we apply to justify or object to such developments?

If we make animal painless we are depriving them of a beneficial physical awareness. We could imagine beings that could be made with limited sentience, only having the perception needed for basic survival, such as for limited self interest for eating, grooming or avoiding injury. In the extreme case we could consider animals made that enjoy being kept in factory style farms, or that want to be eaten, or are even masochistic. These need not be as futuristic as the talking cow portrayed by Douglas Adams' book (1980). We might talk of degrees of pain that could be removed, such as leaving a protective sensation, but instead of it invoking pain, it could just invoke a reflex so that the being would not do injury to itself. It is possible to alter behaviour by control of certain neurotransmitters, such as oxytocin, which is a memory disruptive agent and has been used to remove active avoidance behaviour in animals, that is the animals do not remember painful experiences. Currently, more control can be made using external agents, however, within the next few years of pain and neurobiological research many transgenic animals will

continue to be made. It is very likely that transgenic experiments will be used in pain research. When animals that are painless are produced, which is inevitable, the question will be asked about breeding them.

These type of experiments involve altering the mental requirements of animals to suite our means. We could look at them as beings that would not be able to give their informed consent, though this is never sought from animals or human infants anyway. In fact these futuristic beings could be engineered to give consent. This is not to say that neurobiology is understood now, but it will be in the next decades. The motive is only anthropocentric and the means used are not interested with the life of the animals themselves, however if they did not suffer pain than they could be regarded by many as being better off then beings that do.

If we object to these experiments, we would probably be forced away from arguments based on pain, or preference utilitarianism (Singer 1980), in which sentience, the capacity of a subject for sensation, is the pre-eminent quality on which attitudes towards the treatment of that being by others is based. Some deontologists believe that all creatures capable of suffering, have a general moral right not to be treated cruelly, but this does not preclude their treatment as mere instruments (Feinberg 1980). If we object to these painless animals being made, it may be because we hold religious views according to which we should not "grossly alter the creatures of the earth, or some sort of argument based on it being "unnatural" (Jonas 1966). It could be based on each being having a self, suffering being viewed as the threat to characteristic, worldly related activities which threatens the integrity of the self (Donnelley 1989), as would the removal of sentience. If you don't like the idea of animals being made this way, ask yourself, why not? The Christian view would be that because God gave responsibility to man to look after animals. One must respect other creatures in God's creation and not misuse power (Macer 1990a).

To set out to breed painless animals so that they can then be supposedly used as beings possessing no moral rights is different to the use of "beings" that are born without a brain, anencephalic, or that are painless. There may also be a difference between making a breed of painless animals to using individuals made painless during their ontogeny. An individual that has had some history of feeling pain and is made painless could experience (unless they are made completely nonsentient) either relief or bewilderment. The creation of painless animals in order to make a new class of means for human ends may alter the way we argue about the use of animals. Instead of animals possessing some sort of self integrity, they can be made to be much more the longterm property of humans, not only in commercial terms, or when or how they come into existence, and reproductive choice, but in whether they are sentient animals or a new class of painless animals or "vegemals". Some would argue that this new class would possess the moral status of plants, and they could leave the "normal" animals to roam the pastures, or what is left of the jungles, while using these specially made beings. However, I believe that many would share the view that this would be an unethical use of our power over nature.

It may point to a time when human values, as much as they are regarded by many philosophers as unsound, culturally determined, undefinable feelings, may have a greater place in ethics, either because such creations would be contrary to most people's values, or because of the effect such a creative power would have on our values (Macer 1989). This is a type of view formulated by Kant, in which he

said that we have no direct duties to animals, but if we mistreat them it will remove our feelings to humans. However, it does not always follow, as human tyrants have often been devoted to their pets: we do distinguish between animals and humans, and between friends and enemies. It is useful as an argument when others which are usually stronger, do not apply.

It may be possible to make painless animals, so deeper reasons against the abuse of animals must be examined. It will never be sufficient to justify animal use on the sole grounds of these experimental benefits of using them. We could also gain by human experiments. The justification has to lie on animals having a lower status than humans, but it can still be argued that there are justifiable and unjustifiable uses of animals. In fact the number of animals used in research is less than 0.1% of the animals used and killed by humans. In the face of this we could ask whether genetic engineering poses an extra threat to animals, beyond that of other uses of animals. Genetic engineering may in a few examples allow more potential to change the morphology or internal nature of animals, but there may be other uses of animals which are more unethical. Also the animals changed will be used to improve agricultural strains, so will be part of both "markets" for the use of animals. While changing animals internally offers new problems, we still need to work on the external treatment of animals in general.

There are many commercial uses of animals for testing of what could be called luxury products, such as cosmetics. Each company wants to make a slightly different perfume or soap, and may use animal testing. These tests are objectionable for several reasons, the first one being that they are painful; the second that they are argued to be unnecessary, there are alternative ways of testing using toxicity measurements on cell lines, and the products are very similar to those already on the market, so either are safe enough to use, or not necessary. The only reason they are desired is to make a profit for another business. If companies made the results of their testing known then their competitors would not need to repeat them. Alternative methods are being used to avoid animal use. During the last few years there has been increasing use of products not tested on animals, as a result of consumer purchasing choices.

Genetically engineered animals which are very sensitive to carcinogens, can be used as more sensitive "probes" which would dramatically reduce the number of animals used. It is estimated that "Oncomouse" may lead to some tests for chemical carcinogenicity being compressed from three years to three months. If this is realistic, net costs for experimental animals, as well as the total number of animals used in such studies, will dramatically drop. Another reduction in the number of animals used has been brought about by the use of embryo splitting, which should also be increasingly used. When an embryo is split then the individuals made, 2 -8 in number, are clones, genetically identical. If genetically identical animals are used then the number of animals required in a toxicity test is greatly reduced, as the only difference in treatment and response is attributable to the tested drug. If we are realistic and accept that there will be some animal testing, then at least these techniques will reduce the quantity involved perhaps tenfold. There has also been debate on what sources of animals can be used, especially whether stray dogs and cats can be used for experiments. There are many more stray dogs and cats "put down" than there are animals used in experiments. It would seem better to use them than to breed animals to do experiments on. There are many experiments that do not

require a precise laboratory strain to be used if an alternative exists. However, there has been much public debate, as people say that animals that have experienced being a pet would find it harder to be in a cage. However, many of these animals would probably receive more loving care in a laboratory than they did in the situation they were in before.

Genetic engineering has been used to make vaccines against animal pests, and to protect animals from disease. These could be argued to actually benefit the animals themselves, so be on the positive side. However, there is some inherent opposition to the creation of diseased animals, which some may justify by their potential to advance to medicine. If humans are born that are diseased and some trace can be made to their cause of injury, if the cause can be proven there may be financial compensation at least, however if we make diseased animals it may obtain acclaim from the scientific community for their benefit to scientific and medical research. In fact, some of these animals do advance medicine, and they may not feel much more pain than they otherwise would, but this certainly does not mean it is always justified. In terms of the quantity of pain endured, there is probably less pain than many animals face in factory-style farming. In fact the facilities for care of animals in science is much better than those conditions found in many farms, partly because of the regulations that apply to animals in laboratories that do not apply to farming. The motive for the use of the two types is different, one is for science the other for food, it is not obvious which is the more ethical use of animals. It could be argued that because we have alternative foodstuffs, from plants, the use of animals in medical research is more justified. However, animal rights activists do not usually picket abattoirs.

That is the issue on a broad scale, but what about the individual animals bred for such testing. In the case of clones, they are the same normal animals. In the case of deliberately diseased animals, such as those that develop cancer very easily, or have physical abnormalities bred into them, the question is whether the means justifies the ends. Do we have the right to the actual use of animals, to create in that way, and to bring them into life at all? Numerous "new" animals have been made. There are those that develop cancer, such as the so-called "Oncomouse" that was patented, and numerous other types of genetically modified animal strains, many in mice (Fox et al. 1989). Another example was the addition of the gene for diptheria toxin to a gene expressed only in one cell type in the pancreas (the elastase gene). The toxin was only produced in such cells, killing all that type of pancreatic cell. It is possible to target particular cell lineages to kill them. This allows the study of the animal without those cells. Some of these animals are made to study the genes involved in development, including what are unique models for cancer research.

There have been transgenic mice made as models of the immune system, and a new area of research will be making models to study the nervous system (Hanahan 1989). Embryonic stem cells are used to make some of these genetic modifications and new strains, and there is much research into the genes that control the developmental process (Gossler et al. 1989). The ES cell lines make it easier to control specific genes, for the study of the disease itself and for gene therapy tests. Another area of much scientific interest is their use in studying development, such as for studies in disruption of homeo-box genes. The making of chimeric animals, such as the geep, has been useful for study of the immunological development of the embryo, and rejection mechanisms. There are also major questions such as the fate

of each cell as the embryo tissues develop, and the processes of the immune system in developing self-tolerance. The ES cell lines also offer ways to study many new mutations. They have advantages over other methods of making transgenic animals, in the precision of gene insertion possible by homologous recombination, in the simultaneous screening of mutants. Although at this stage other methods of gene insertion have wider species application, they have been made for several species, so should be possible in others when attempted. Their advantage in agriculture, would be the increased sense of safety, from the precision offered.

Transgenic studies after incorporating growth hormone genes into pigs and sheep have not shown any relation between gene number and expression of genes and growth rate. In fact many of the pigs died within 90 days of birth in the preliminary experiments, with significant problems of lethargy, muscle weakness, incoordination, and susceptibility to stress (Lamming 1988). Most of the transgenic animals did express much more growth hormone, and did have improved weight gain (about 10%), but also had gastric ulcers, dermatitis, nephritis and other major problems. This does illustrate the problems, and until these factors can be removed even if it was economic to use these animals, it would not be ethical if they are going to suffer. Research into new genes and techniques continue (Pursel et al. 1989). There have been pigs made that are not sick, but grow faster.

There have been several surveys about the reason animals are used in medical experiments. The researchers have only begun to realise that they have to publicise the benefits of their projects to counter the strong pressure from the antivivisection lobby (CSA 1989, Loeb 1989). The use of animals in research, or agriculture is based on the use of animals by mankind, since our origins. It assumes we can dominate animals when necessary for the improvement of human living standards. This is based on the starting point that humans are of higher status than animals. If we reject this, then we will probably oppose human uses of animals. There have been considerable numbers of studies done on particular animals, the mouse and the rat are the most common, and should become more so with the higher maintenance costs of larger animals and the lower level of public sympathy for mice or rats. In medicine they have been used for general biology, transplant studies, for risk assessment of potential carcinogens, for human disease models and behavioural studies (Gill et al. 1989). Their use will continue, but substitutes will be found.

Regulations

Animals that are genetically modified will probably come under some type of regulation. In many cases it may be only in regard to the laboratory maintenance or experiments on them, rather than their creation itself. In Britain transgenic animals can now only be made under license from the Health and Safety Executive (Connor 1989). The Committee recommended that the license should cover the breeding of transgenic animals until it can be demonstrated that the progeny are not likely to suffer adverse affects (HSE 1989). The Animals (Scientific Procedures) Act 1986, regulates "any experiment or other scientific procedure applied to a protected animal which may have the effect of causing the animal pain, suffering, distress or lasting harm". This applies to the creation of new varieties made by genetic engineering techniques. It is important to consider the last part of that sentence, "lasting harm",

which is a characteristic of animals made as models of human disease.

It is a common misconception that genetic engineering will try to increase the size of animals. In most cases smaller animals are desired as they are cheaper to maintain. Chickens and pigs have become smaller recently (Seidel 1986). What is desired is rapid growth rate, or turnover. This also means that the average age of farm animals will decrease, and this is a trend that has been occurring as younger animals are more efficient, such as egg-laying hens or dairy cattle. In addition to increasing growth rate, other agricultural aims include decreasing water dependence, increasing drug resistance and disease resistance. Some of the effects could be neutral such as controlled increase of size, or altering fat/protein balance, or altering forage requirements, and the quality of products such as eggs or wool, but each case should be examined. Dairy cows in the 1980's produce 2.5 times more milk than those in the 1940's. The use of genetic engineering will be able to more dramatically change the metabolic characteristics of animals.

There has been a very useful evaluation of research procedures, so that only those which are judged to be ethical are pursued. This has saved much animal abuse, and a limit will be reached at which only ethical uses of animals are permitted. The humane treatment of animals requires that if alternatives do exist to obtain a satisfactory result than we use that method. Alternatives involve reducing the number, refinement of procedures so there is less suffering, or replacement of animals (Smith 1988). Alternatives include using *in vitro* experiments, using cell lines, or embryos of lower status or larvae, or isolated organs, and computer simulation. The urgency of the research needs to be reassessed.

Government regulations that require animal testing of new drugs and compounds need to move with the development of alternatives. Often much animal experimentation is done because of regulations protecting humans from unforseen effects of drugs or new medical therapy. One step is for alternatives to be quickly developed, tested and accepted. Another step is to limit the duplication of commercial products, including pharmaceuticals. There need to be alternatives developed in toxicity testing, which is not only more ethical but more economic (Goldberg & Frazier 1989). In this respect new genetic techniques and embryo manipulation will reduce the number of animals used in vivisection. If we place much higher value on humans than the experimental animals, such as mice or rats, then we will use animals to test drugs to protect humans from any ill-effects (Cohen 1986), but only within limits. It is consistent to use lower organisms if possible, and also to use human volunteers and epidemiological research.

Food animal farms house the vast majority of animals used by humans. The attention given to animal rights by experimental use of animals has also shifted attention to the practise in farming. Principle concerns include confinement of veal calves, pigs and poultry in small cages. There have been several countries which have banned the use of battery caged hens. It has been illegal to make battery cages in Switzerland since 1981, and their use will be illegal from 1992. In Sweden they will be illegal from 1998. There are new rules in the U.S. Department of Agriculture for the care of guinea pigs, hamsters and rabbits, from July 1990. However, the rules have some flexibility, so that laboratories will not need to buy new cages. They can do things, such as build tubes to connect hamster cages so that they are happier, because they can run around. It will be based on the use of performance tests to check if the animals are happy, which could be very hard to

judge. These regulations reflect much public objection to practises that are seen to be cruel, and which can be avoided at little extra cost (Nicol & Dawkins 1990). It is still possible to use contained areas for farming, but greater space in required. This may be important in the containment facilities that are given to genetically modified animals, and also reflects the growing influence of animal welfare concerns in different countries.

If society changes its philosophy of animal use it should know the consequences of any change. If people do not want to grow animals for food than they have to eat vegetables. If they do not want to use animals for some medical research than they should not expect such rapid advance in the treatment of disease. There needs to be education about the consequences of altering the way we treat animals. People need to decide how much more they are prepared to pay for better treatment of animals, such as the costs of eliminating battery farming, or the costs in not using new animal treatments that produce cheaper milk or meat such as bovine somatotropin. The consequences on the different communities involved in agriculture of these decisions also needs to be considered, a variety of external factors, some of which will be discussed later.

7. Applied Genetic Engineering

Industrial Applications of GMOs

Microbial Production of Biochemicals

There is no major ethical debate about the use of microorganisms to produce products ranging from industrial chemicals to alcohol. Microorganisms, because of their size, life habits and versatility have long been used for the production of both simple chemicals and complex brews. In the last decade the long history of human use of microorganisms has been extended as genetically engineered bacteria and yeasts have become commonly used. Bacteria and fungi are being used for the production of an increasing variety of commercially important products.

Protein Engineering

Organisms can be made to produce new products, and/or made to grow under different and sometimes extreme conditions. Bacteria that can grow in a 70% solution of toluene, and in a high concentration of other organic solvents, could be useful for industrial reactions requiring those conditions. Thermophilic bacteria, that can grow at 100°C, and the enzymes that they produce, are useful for industry. Reactions proceed faster at higher temperatures and thus genes being isolated from thermophilic bacteria and transferred to other organisms will improve production.

There are a great variety of naturally occurring proteins to be exploited. The genes can also be altered, which further expands the potential of the new technology. Protein engineering allows specific alterations to be made using a technique called site-directed mutagenesis, where specific DNA sequences in genes can be changed. Modified proteins can be made, which can alter the catalytic properties of natural enzymes, or the stability, or the antigenicity of proteins.

Scientists have made a new enzyme completely synthetically, opening up the possibility of designer enzymes. Stewart, Kahn and Klis of the University of Colorado Medical School have designed an enzyme on a computer screen, then produced the 73 amino acid enzyme, chymohelizyme-1, in the laboratory and studied the biochemical properties. The enzyme displayed the expected biochemical properties, and it is based on the naturally occuring enzyme chymotrypsin (Amato 1990). It opens the way for many future possible constructions of novel enzymes.

Production of Chemicals

Microorganisms have been, and will continue to be, used for the production of many chemicals. They have also been made to produce enzymes for industrial use (Imanaka 1986). Enzymes are the catalysts that carry out all the synthetic and degradative reactions of living organisms. The enzymes produced from

microorganisms are particularly suitable for commercial applications (Neidleman 1989). The world market for enzymes was worth more than US$ 500 million in 1985, and is expanding as only a fraction of the enzymes existing in nature have been characterised. One everyday use of a genetically engineered product is of the enzyme lipase (there are many different types), which breaks down fat, and is added to washing powders, so that the amount of washing powder needed is greatly reduced.

Genetic engineering is being used for the production of compounds for cosmetics, especially in Japan where the industry is already promoting "bio-cosmetics" (Scheidegger 1989).

Any organism that can be grown in cultivation can be used as a source of materials for human use. The range of materials can be diversified by genetic engineering. Within ethical limits, the best production system will be one that is cheapest to produce good quality product. There should be use of organisms that are primary producers, that is plants, because the energy conversion is most efficient. An example of an alternative system that could be explored is the use of algae that can grow in saline water, such as Dunaliella. It is currently used for production of carotene and glycerol, and may be grown cheaply in shallow pools of salty water with a few nutrients, open to the sun (Ben-Amotz & Avron 1990). This culture system presents a cheap way of producing proteins, and since it is a eucaryote it will be able to produce eucaroytic proteins that are processed properly. The feature of genetic engineering is that it allows any organism to be used, and researchers should target attention on organisms that will be the most cost efficient, and ones which can be used with little technological complication.

Medical Drugs, Proteins and Vaccines

Microorganisms have been used for the production of medically important drugs such as antibiotics. With the advent of recombinant DNA techniques this role has greatly expanded. The genes that direct the synthesis of mammalian proteins have been inserted into bacteria, which are then grown in large cultures, to produce large quantities of medically important proteins at low cost. The availability of these products makes therapies for many previously untreated or uncured diseases possible (Clark & Kamen 1987). It would not be an overstatement to say that they have and are revolutionising the treatment of disease. Many human proteins are now being commercially manufactured using this technology. These include blood clotting factor VIII, interferons, iInterleukins, growth hormone, erythropoietin, insulin, tissue plasminogen activator (TPA) and various growth factors, which have medical uses (Gilbert & Villa-Komaroff 1980, Anderson & Diacumakos 1981, PMA 1988). They can be produced in yields of several grams per litre of broth, in bacteria such as Escherichia coli (Davies 1988).

Recombinant DNA techniques are being used to produce human vaccines. A vaccine against Hepatitis B has already been approved for worldwide use (Zuckerman 1988), and it costs about US$ 1 per dose. There has been much research on preparing vaccines against malaria, AIDS, and other major diseases, and there are vaccines under trial for some. Many pharmaceutical products can potentially be made (Vane & Cuatrecasas 1984). Unfortunately there is relatively little investment in research by the pharmaceutical industry, as vaccines account for less than 1% of their profit, but a greater percentage of their liability (Bloom 1989).

Veterinary drugs and vaccines have been made (Van Brunt 1987b, Bishop 1988). They have been produced even for diseases that were impossible to vaccinate against previously, such as tapeworms in sheep (Anderson 1989). Rabies vaccine is in widespread use in France, and Belgium, though regulatory delays in the USA have meant it only began field trials in August 1990.

Use of Fungi

Fungi are commercially important in producing compounds such as penicillin and other antibiotics. Fungi are also used as food, or for food additives, such as citric acid, and beverages such as beer or wine. As in bacteria, individual genes and even base sequences can be altered, allowing precise genetic control. Like bacteria, they have potential for producing many substances (Timberlake & Marshall 1989).

There are many possible improvements to be made in processes with a long history of microbial use, such as malting and brewing (Wettstein 1989, Chater 1990). This could be done by improving secretion efficiency, or relieving rate limiting steps in metabolic pathways.

Using Plants and Animals

Mammalian Cell Culture

There are new developments which may allow the use of mammalian tissue culture cells in commercial ways. Recently mammalian cells have been used to produce useful protein products (Ramabhadran 1987). Some eucaryotic proteins made by bacteria are not biologically active because bacteria lack the mechanisms to modify newly synthesised proteins in order to activate them. Fungi such as yeast are being used, as the current best production obtainable from mammalian cells is still an order of magnitude (one tenth) below that in the best bacterial systems (Friedman et al. 1989), though this may be sufficient for commercial production in some cases.

Plant Cell Culture

Plant cell tissue culture is being used to produce plant-derived products. The first tissue culture product commercialised was Shikonin, a dye and pharmaceutical manufactured by Mitsui Ltd. in Japan, in 1983. Ginseng, one of the most valuable plant products, can be harvested only after 5-6 years of plant growth, and the plant is destroyed. Large yields have been produced by culture of chlorophyll-accumulating aggregates of ginseng cells (Odnevall & Bjork 1989). These two examples did not use genetic engineering techniques, which will expand the range enormously. The technology is still at an early stage, and many pharmaceutical products can be produced (approximately a quarter of all pharmaceuticals are plant-derived) (Fowler et al. 1988). The advantage of using plant tissue culture is that factory control makes the supply independent of seasonal plant yields or imports.

Use of Whole Plants

Transgenic plants are also being used to produce industrial products. Very recently two American biotechnology companies have begun to use plants to produce melanin, the natural pigment that darkens skin. This will be used in new sunscreen lotions (Buck 1989). There have also been pharmaceutical peptides produced in oilseed rape plants. Some of these proteins could be economically

produced in the seeds of plants (Gasser & Fraley 1989). There is much research interest in the production of thaumuatin, one of the sweetest known substances. It is normally extracted from a West African plant, however, the gene has been isolated. For example, in New Zealand the gene has been transferred to potatoes, with the idea of using potato as a source of supply. Thaumatin is already used as a food additive to increase weight gain in pigs by making them eat more of the nicer tasting sweet food (Witty 1990). If thaumatin is included in the crops directly it will be simpler. Also, the worldwide market for human low calorie sweeteners is over US$ 3 billion annually, so there is much possibility for entering this market with a lower cost product.

Human serum albumin has been produced in potato and tobacco plants (Sijmons et al. 1990). Animal antibodies have been produced in transgenic plants (Hiatt et al. 1989), and this could bring the cost of producing monoclonal antibodies down by a factor of 10,000 (Hiatt 1990). Animal antibodies could also be used to protect plants against viral diseases, or the antibodies could be used to scavenge small organic pollutants such as toxins, from the environment. Obviously, the potential range of proteins is enormous.

Biopolymers

Bacteria can be used to produce polymers that can be processed into polypropylene-like plastic. Biopolymers can be made using the precise enzymatic control that is not possible to use with synthetic polymers, with the advantage of biodegradibility to avoid pollution problems. New types of products, like synthetic rubbers, are also objectives of this research. Bacteria can also be made to produce the raw material for biodegradable plastic bags. The genes for polymer production may be put into foodcrops, such as potato tubers. This would also avoid using nonrenewable and energy intensive production techniques. This research area is attracting much commercial research, and it is already feasible to produce industrially one type of polymer, based on polyhydroxybutyrate, as a speciality plastic. It will take further work before bioplastics can compete financially for the commodity plastic market (Pool 1989).

There is also research into developing a process for converting food wastes, such as potato peels, into a source for biodegradable plastics. The food waste is converted to glucose, then into lactic acid, which is used as a feedstock for biopolymers.

Animals as Bioreactors

There are experiments underway to use animals to produce desired proteins in their milk, as protein factories or "bioreactors". Currently there has only been reasonable success using sheep which make human blood-clotting factor IX or human alpha-1 antitrypsin. The protein alpha-1 antitrypsin can be used to treat emphysema, a lung disorder caused by a deficiency of this protein. There are advantages to use of bioreactors over bacteria for producing proteins, as many proteins require processing by mammalian enzymes after initial protein synthesis. The mammary gland is very useful, as in sheep about 400 litres can be collected per lactation cycle (in cattle the figure is 8000 litres) (Clark et al. 1989). The production of transgenic sheep and the subsequent breeding of a flock of sheep probably costs

about US$ 1 million, which is much cheaper than establishment of an industrial genetic engineering plant.

However, sheep take a relatively long time to grow in order to test expression, whereas mice produce only small quantities of milk, and rabbits have a useful ratio of size versus development time. Transgenic rabbits have been made that produce biologically active human interleukin-2 in their milk (Buhler et al. 1990). The milk yield from rabbits is about 100g per day, with a three fold greater protein level than cow's milk. Also rabbits are cheap, and can be housed in an enclosed and controlled environment.

Amgen, a Californian company, is designing chickens that will lay eggs in which the normal protein, albumin, is replaced by precious drugs. From 10 chickens it may be possible to produce a gram of interferon daily, a very large quantity (Hill 1989). Silkworm caterpillars have been modified to produce human insulin, but this is still to be developed commercially.

Production of Biomass

Lignocellulose is the most available renewable resource for the production of food, fuel and chemicals. Approximately 2×10^{11} tons of carbon are fixed every year as plant biomass through photosynthesis. Biomass consists primarily of cellulose, hemicellulose and lignin, and there is about a 100 fold excess of it over current uses as animal feeds. There has been much research on the microbial conversion of these polymers, and there has been conversion of this material to protein. Genetic manipulation has been used to transfer enzymes into microorganisms, to enhance their ability to degrade polymers to usable products (Srinivisan & Cary 1988). There is much potential for additional uses of this resource for many purposes, and it is important in view of the desire to move to renewable resources and environmentally friendly technology.

Agricultural Uses of Plant Genetic Engineering

Expanding Plant Breeding

For millenium plants and animals have been selectively bred to develop varieties that are more productive, or suitable for human use. The welfare of humanity is inextricably bound up with efficient agriculture. Plant breeding as a science began in the 19th century after the discoveries of how plant traits are inherited (Simmonds 1979). Our modern varieties originated from gene transfers within crop species, by selective breeding. There are, however, some major exceptions. For example, about 5,000 years ago wheat was created, when the three genomes of Triticum monococcum, Triticum tauschii, and a species of Aegilops came to be combined. The definition of a species rests on the concept of genetic isolation but sexual exchange of genes between species can and does occur in nature without human intervention.

Often, the crop species does not contain sufficient genetic diversity to allow the desired improvements, hence the search for diversity has led plant breeders to use new genetic technology (Goodman et al. 1987). The same concern has led animal breeders to use the same technology, as well as a desire to increase the desirable traits beyond those obtainable by normal breeding. In both cases, the aim

is to arrive at a breeding population consistently expressing the desired trait(s). One of the main weaknesses of conventional plant breeding is its dependency upon sexual crosses and thus to genes that exist only in one species.

There are dozens of examples of agriculturally important genes and traits transferred to crop plants by interspecific or intergenic hybridisation and they have been reviewed by several authors (Goodman et al. 1987, Gasser & Fraley 1989). Recombinant DNA technology allows the transcendence of inter-species barriers and makes very novel genetic combinations possible. The first transgenic plants were created in 1983. One of the most popular methods of gene transfer is the use of the soil bacterium Agrobacterium tumefaciens, which can transfer genes to many plants at wound sites. However, it works mainly on the dicotyledonous plants which excludes many crop plants, such as cereals. Direct DNA transfer can be used to transfer genes to protoplasts (cells which lack a cell wall) from which plants can be regenerated. About 150 species of plants have already been regenerated from protoplasts, so the potential application of the technique is already very large.

Among the techniques for gene transfer another common one is "biolistics", the use of particle guns to shoot DNA into cells. Some techniques use tungsten particles, or gold beads. There may also be advantages of up to a 40% reduction in time for crop production via some biolistic based approaches over using Agrobacterium (Christou et al. 1990). This approach has recently been used to transform corn, and for the first time to produce genetically-modified fertile corn. The gene for resistance to the herbicide bialaphos has been inserted and the corn are resistant (Gordon-Kamm et al. 1990). Rice and corn are the only major crops that have been genetically modified to produce fertile transgenic offspring. Further improvements should be expected and developed, and the final proof of success must wait until field studies are completed. Microinjection has also got potential (Potrykus 1989).

Gene transfer technology has advanced at a far faster pace than our understanding of plant biotechnology and the factors which are important within the plant in determining other useful agronomic traits. Because of this, attention has been focused largely on characters which might be determined by single genes (Walden 1989).

The main focus of most biotechnology programmes is to produce new cultivars with improved pest and disease resistance to promote more environmentally acceptable alternatives for food production. Yield is no longer the only goal, improving the quality and marketing appeal, using genetically engineered pest and disease resistance to produce healthier products, are goals. Traditional methods of cross-breeding are not only limited, but slow and costly (Sansavini 1989). Transgenic plants are also being used to study gene expression and control, which will be useful for further practical applications (Benfey & Chua 1989).

Plant Disease Resistance

Natural disease resistance is complicated. Plant breeders have long sought to increase the disease resistance of crops through selection of resistant varieties and by hybridising crops with wild relatives. About one third of total crop losses are directly attributable to plant disease. Molecular techniques, such as insertion of antiviral or antibacterial genes from other species into plants, and cellular methods to allow rapid screening for the desired phenotype, have led to more rapid progress.

Plant viruses are not well understood, but opportunities for improved disease resistance exist as the plant-pathogen relationship is easier to modify (Wilson 1989).

Viruses cause serious diseases in many crops. The genetic basis of viral resistance in plants is narrow, so resistance breaking strains of virus frequently appear. Isolating the plant's own resistance genes to combat disease is not practical until they have been isolated. The function of such genes depends on complex factors, such as the right genomic background. However, they could be used as good starting materials for protein engineering. Good viral disease control has been obtained using three different approaches:

* **Cross protection** occurs when plants are deliberately inoculated with a mild strain of virus. The plants are then resistant to infection with normal virulent strains of the same virus. Cross protection is probably due to the presence of the coat protein of the protecting strain. Coat protein genes of several viruses have been inserted into transgenic plants to provide protection (Fraser 1989). The expression of a single coat protein gene can protect a plant against several different viruses. This heterologous protection is important, as it reduces the number of genes required for multiple viral resistance. This has protected crops from infections of alfalfa mosaic virus, cucumber mosaic virus, potato viruses X and Y, soybean mosaic virus, tobacco mosaic virus, tobacco rattle virus (Conner et al. 1990), and others. Importantly, it has been found that transgenic plants that express the coat protein genes of tobacco mosaic virus or alfalfa mosaic virus also have some protection against other viruses. The mechanism of this protection is unknown (Anderson et al. 1989).

***Insertion of satellite viruses** (which are unable to replicate themselves) into the plants' genome to provide protection has been used for cucumber mosaic virus and tobacco ringspot virus (Conner et al. 1990).

***Antisense RNA**; the translation of a specific mRNA can be inhibited if the plant contains a complementary antisense RNA, which will form a double-stranded RNA molecule with part of the messenger mRNA, preventing translation of the protein, and thus protecting the plant (Day 1989).

Tobacco plants that have been made resistant to tobacco mosaic virus (TMV) infection (Abel et al. 1986), are of great commercial importance. Cotton plants have successfully expressed genetically transferred marker enzymes, and commercially important genes are being tested. Douglas fir has also expressed marker genes, and the seedlings were micropropagated from shoots. The importance of forestry trees is very high, and disease resistance genes are perhaps the most immediate targets. There have also been genes inserted into tobacco, cotton, corn and soybeans to make them resistant to crown gall disease (OTA 1988b).

Potato is one of the most important stable food crops worldwide. Because it is a tetraploid it is laborious to use traditional breeding to improve varieties. Viral diseases are of major importance: potato virus X can cause yield depressions of over 10%, and potato virus Y can decrease yields by up to 80%. Thus virus resistance holds a major key to potato crop improvement. Potato plants containing resistance genes to these viruses, have been tested in many countries for several years. The

inserted genes may not affect other cultivar characteristics. Current work is aimed at obtaining simultaneous resistance to more of the major viruses (Elzen et al. 1989). One team in Monsanto has generated resistance to both virus X and Y in a commercial potato variety, Russet Burbank (Lawson et al. 1990).

Bacteria can be used for disease resistance. In 1988 a bacterial fungicide called "Dagger G" was introduced for the control of cotton diseases caused by Rhizoctonia and Pythium. It was given approval in the USA by the EPA after only five months. This is in contrast to the common ten year period required for approval of chemicals. Dagger G should have fewer negative side effects than chemicals and will probably be improved by genetic modification.

Pest-Resistant Plants

The current pesticide market in the United States is worth US$ 3 billion annually. There are many problems associated with pesticide use, including pest resistance to chemicals and negative environmental effects. There are also insecticides being developed that are of plant origin (Arnason et al. 1989).

Biocontrol

Biological pest control has a long history and is becoming more important (Campbell 1989). In 1889 Vedalia beetles were introduced to California to control cottony cushion scale in citrus orchards. They are still being used. In recent years imported parasitic wasps have been used to control alfalfa weevils. Another example is the introduction of musk thistle weevil which is a long term alternative to chemical herbicide for the control of musk thistle. It has been well used in North America (Cramer 1989). Another is the Ecogen product "Collego", for controlling northern gointretch, a costly weed for rice farmers. It is a dry formulation of a naturally occurring fungus. There are other similar products on the market, and more are being developed.

Crop rotation and tillage that disrupt pest life cycles are at the first level of control. At the second level is the introduction of self-sustaining control agents. Expansion of the marketing of biocontrol agents by major companies has been slow, as they will lose much profit from the sale of chemicals. There has been more introduction of repeated application of biological pest control, such as bacteria or fungi-based pesticides (Cramer 1989). Pests take longer to develop resistance to biocontrols, and although the results may take longer to see then with chemicals, the management can be long term. They have the additional advantage of specificity, not seen with insecticidal chemicals.

Insecticidal Proteins

Plants expressing the insecticidal protein of a bacterium, Bacillus thuringiensis are pest resistant. Insect pests will die if they eat the plants. Larvae of moths and butterflies can be selectively killed by different insecticidal proteins. Many companies have put this gene into crop plants including corn, cotton, soybean, tobacco and tomato and this protected the plants from insect larvae (Buck 1989, Cramer 1989). Some crops such as cotton may normally have over ten applications of insecticide over the growing season. The Belgium company Plant Genetic Systems which has been testing plants expressing insecticidal proteins since 1986 has found the resistance to be very good without affecting yield. Like several

US companies, including Monsanto, they will be producing several commercial varieties soon.

The control of caterpillar pests with plants expressing this insecticidal gene offers several advantages. Control is independent of the weather, and in conditions which would be unsuitable for spraying chemicals or bacteria, the crop is still protected. All parts of the plant are protected, such as the roots, or new growth previously susceptible between sprayings (Meeusen & Warren 1989). The pests are affected as soon as they begin to feed. Broad spectrum insecticides kill all insects, which includes spiders and beetles which are useful predators. The B. thuringiensis endotoxin kills only killing leaf-eating species. Different insecticidal proteins have been expressed to kill larvae of Lepidoptera (moths) and Coleoptera (beetles). There are different proteins produced by different strains with varying specificity. Being proteins, they are biodegradable (Gould 1988), and can be much cheaper to develop, and to obtain environmental release approval for use. To develop and register a new chemical insecticide costs about US$ 25 million, but to develop a new plant variety costs about US$ 1 million. However, the Environmental Protection Agency (EPA) regulations may require that a new crop variety needs to be registered as a pesticide in the USA, which would add about US$ 10 million to the cost (Meeusen & Warren 1989). The situation remains uncertain, and test crops are under review.

Digestive Inhibitors

An alternative way to control herbivorous insect pests is by introducing the gene for digestive protease inhibitors into the plants, so the animals cannot digest food. The expression of these plant genes, which are thought to be a defensive response to insect attack, can be enhanced. Wounded plants produce a factor which induces the synthesis of protease inhibitors specific against insect and microbial proteases. They have an effect on a wide range of insects and are known not to be harmful to humans (Waldman 1989). The big environmental advantage is that only insects that eat the plants are affected. Commercial seed are soon expected to be available. The first field tests in Belgium were in 1985. In New Zealand, researchers are trying to identify the best plant protease inhibitors for insertion into clover or pasture crops, there is also work using insecticidal proteins to improve pest resistance in clover.

Insecticidal Microorganisms

There has also been work on the development of insecticidal microorganisms to be sprayed onto plants. The current application costs of spraying microorganisms containing a toxin gene are similar to the costs of applying chemicals, but with the significant environmental advantages. These need continual application, but may not require additional regulatory approval for human consumption, as they will need to be if they contain novel genes. Losses to crops also occur during storage after harvest. It is possible that increased levels of antifeedant could be added to plants to reduce such losses.

Herbicide Tolerance and Weed Control

The use of agrochemicals is still expanding. Weeds reduce crop productivity by at least 12%. Overall worldwide sales of herbicides are worth over $US 5 billion

annually, and are double the market for insecticides, and fungicides. Even in developing countries where labour for weed control is very cheap, large quantities of herbicides are used. The effects of this large-scale chemical use are still unknown, and many effects are indirect. The function of soil ecosystems is poorly understood, and the major biological cycles of organic matter breakdown and nitrification are the most sensitive to these chemicals (Edwards 1989).

Genes that give plants tolerance to herbicides have been isolated and incorporated into some plants (Shields 1985, Shah et al. 1986). There has been a variety of herbicide resistant plants developed, and there are some recent reviews on this (Mazur & Falco 1989, Schulz et al. 1990). Work has concentrated on herbicides that are more environmentally friendly than those commonly used. The gene from bacteria that confers resistance to the herbicide glyphosate (Roundup) has been expressed in higher plant chloroplasts (Cioppa et al. 1987). Since 1987 tomato plants expressing the gene, have been made (Fillatti et al. 1987). The gene is under patent by an American company Calgene, and is called "GlyphoTol". It has also been tested in cotton (OTA 1988b) and has been transferred to many other crops.

Resistance to sulfonyl-urea compounds, the active ingredients in Glean and Oust herbicides, has been obtained by the introduction of a mutant acetolactate synthase gene. Many researchers have transferred the gene to a wide range of plants. Plants resistant to phosphinothricin (Basta), have also been made by Plant Genetic Systems. Potato and tomato plants that can grow with concentrations of herbicide ten times higher than normal herbicide application level have been grown (Newark 1987). The field can be sprayed to kill weeds without affecting the crops. The results indicate there is no yield penalty. Many field trials have been conducted. Resistance to other herbicides such as atrazine (AAtrex) is also being developed.

There are different ways to alter herbicide tolerance and a recent comprehensive review by Schulz et al. (1990) summarises these. Sensitive enzymes can be over-expressed, by increasing the copy number and/or the expression of the gene. It therefore requires more herbicide to kill the plant. Site-directed mutagenesis can be used to alter the herbicide binding to enzymes. The herbicide uptake can be reduced by altering transport systems or the morphological changes such as increasing the number of cuticular wax layers obstructing penetration of the herbicide. Enzymes that degrade the herbicide can be expressed, and this approach has been effective against bromoxynil, phosphinothricin and 2,4-D (Conner et al. 1990, Schulz et al. 1990).

Research has mainly been conducted on those herbicides with properties such as high unit activity, low toxicity, low soil mobility, and rapid biodegradation and with broad spectrum activity against various weeds. The development of crop plants that are more tolerant to such herbicides should prove more effective, less costly and more environmentally attractive weed control. The commercial strategy for chemical companies is to gain increasing market share through a shift in herbicide use, not to increase overall use (Gasser & Fraley 1989). Herbicide tolerant plants will have the positive impact of reducing the overall herbicide use and will also lead to substitution by more effective and environmentally acceptable products. The first herbicide resistant crop to be released for use was atrazine-resistant Canola (Mazur & Falco 1989). Imidazolinone resistant corn and sulfonylurea resistant soybeans and potatoes are under evaluation. The technology is widely applicable, so once the food is judged to be safe, a large range of crops

may be available.

It is possible to use phenotypic selection to attempt to develop herbicide-tolerant crop cultivars. Cellular selection has often been used, but the whole plant response can be different to the cellular response. Phenotypic recurrent selection has been used to select for 2,4-D tolerance in red clover. The levels of 2,4-D tolerance were increased by 35% over four cycles (Taylor et al 1989). This is an alternative to gene insertion. The advantage is that the gene is found "naturally" in that species. The Soybean variety, Tracy M, was bred by classical means for resistance to the herbicide Metribuzin (Schulz et al. 1990). However, this sort of selection method is not necessarily intrinsically safer for animal or human consumption. We need to look at genetic engineering as an extension of traditional crop breeding goals. All alternatives are potentially useful.

There are several advantages of herbicide tolerant plants (Conner et al. 1990). The obvious use is in removing weeds from crops. It also allows the maintenance of genetic purity during seed multiplication of new cultivars. It could allow chemical thinning of crops after the mixing of parent and resistant seeds. It can also be linked to other characters, as a selection method. There is no need to apply herbicides until weed infestation reaches an intolerable level, therefore less herbicide is used. This reduces soil erosion. A single safe herbicide can be used instead of a mixture of herbicides, reducing the chance of weeds becoming resistant to several herbicides.

Better Crop Varieties

The most obvious improvement accomplished by traditional breeding is increased yield. In the USA from 1930-1975 the average yield per unit land increased by the following percentages: soybeans 70%, wheat 115%, corn 320%, and grain sorghum 358%. This increase was accomplished by small increments, but genetic engineering techniques have the potential to rapidly increase yield, as they complement the traditional technology. In the USA the average annual increase in corn yield is 1%, however, in parts of southeast Asia where more people live the rice yield is no longer increasing. This presents problems that will require new approaches to improving yield. During the Green Revolution the average rice yield increased 4% annually, but principally by converting stalk to seed. There is much potential to increase yield, for example by improving the efficiency of photosynthesis so that more carbon is fixed into plant material. There are efforts to alter the cell membranes of plants, as well as basic enzymes involved in photosynthesis, to increase the efficiency of plant growth. Any approach must also involve the associated good farming practise.

Tolerance of Environmental Extremes

Plants may be able to be more resistant to drought, flooding, salinity or sensitivity to heavy metals, so that they can be grown in areas of the earth currently beyond the tolerance range of species, or even those areas unable to be used for agriculture at all. About 30% of the world's land area has major plant stress conditions, including insufficient soil nutrients or water, or toxic excesses of minerals and salts. To exploit other environments, tolerance to low temperature is also important. The antifreeze gene from an arctic fish has been transferred to soybean, with the goal of creating plants tolerant to low temperature. There is

research by a number of groups on the development of aluminium resistance in plants. Aluminium toxicity is a problem in low pH soils, where it may reduce plant growth. By making plants tolerant, they will grow better in such soils.

Pine trees are being made more drought resistant and suited to warmer weather, because of the expected climatic changes due to global warming expected in North America in 30 or 40 years when the trees mature. Due to the long reproductive cycle, and the need to wait 20-30 years before mature traits can be evaluated, we are now using only the second and third generations of genetically improved trees. The long juvenile periods, large size and high natural heterozygosity limit the application of conventional breeding techniques, so genetic engineering is more applicable to tree improvement than to herbaceous agronomic crops. The traits that will be targeted include climatic adaptation, fusiform rust resistance (losses exceed US$ 100 million a year), and herbicide resistance to allow better plantation establishment. There are other long term targets such as nitrogen fixation, lignin biosynthesis, cellulose biosynthesis, photosynthetic efficiency, cytoplasmic male sterility, and apical dominance (Olsen 1988).

Nitrogen Fixation

A major long term project for crop improvement is to characterise, then transfer, the genes for nitrogen fixation into plants to enable them to fix atmospheric nitrogen to save using nitrogen fertilisers. However, the nitrogen fixing pathway involves 17 different genes and regulation is important. The transfer of the unit of 17 linked genes has been done from Rhizobium to Aztobacter strains. The strains could then fix atmospheric nitrogen. To fix nitrogen for plants, there is also the requirement to have the genes for a symbiotic relationship between the legume and the symbiont (Paul & Clark 1989). The importance of this technology is highlighted by the growing pollution of ground water by nitrogenous fertilisers. Expensive biological and mechanical filtering to remove nitrates from drinking water is the current "solution". The only success has been in improving the nitrogen fixing ability of some Rhizobium strains. It is a much more distant goal to insert the genes into plants in a way in which they could be used (Postgate 1990). In terms of economics, the market for a nitrogen-fixing crop plant would probably be small in the developed world. The advantages for the third world would be greater, saving the costs of importing chemical fertilisers.

Improved Nutritional Qualities

The food content of seeds, and plant products can be altered to improve their nutritional qualities. New techniques are continually being developed. One such technology involves using antisense RNA sequences to bind to the mRNAs of undesired proteins. One application was the reduction of the concentration of an enzyme (polygalacturonase) which is produced by ripening tomatos causing softening of the tomato. The concentration of this enzyme was reduced by 99%, so the fruit stay firm (Day 1989). These tomatoes have been developed to improve shelf life (about 300% longer) and taste since growers can leave the tomatoes on the plant longer (Kramer et al. 1989). These tomatos are being patented by Calgene, and are currently under consideration for FDA approval for human consumption. There is work in New Zealand on the control of ripening and softening in apples. The goals are to improve storage life, as well as quality (texture, colour, and sugar

content).

Entirely synthetic proteins have been designed to supplement the overall production of essential amino acids in potatoes. The appropriate DNA sequence can be designed and synthesised in the laboratory, then inserted into the crop (Jaynes et al. 1986). Insertion of an artificial gene coding for a protein rich in essential amino acids can reduce from 1.8 to 0.8 kg the amount of potato one must eat each day to get all the daily protein intake (Dodds 1988). In CSIRO, Australia and DSIR, New Zealand, pea albumin (which has many sulphur amino acids) is being inserted into white clover, so that it will lead to better wool growth in the sheep that feed on the improved clover. Improving the amount of methionine-rich protein in plants is important for other animal based systems also.

Widening Consumer Choice

There is work at the DSIR, in New Zealand, on introducing new characteristics to increase the number of varieties of kiwifruit. These include altering internal colour, texture, seed content and shape, and making smooth skin. There are also goals involving nutritional characteristics such as altering sweetness and increasing vitamin C. The aim is to introduce new varieties for consumer choice. There is also work on improving the flavour of onions (Conner et al. 1990, Macer 1990b). As discussed later, this type of food product requires examination before being used for human consumption.

Ornamental Plants

There have also been advances in the breeding of ornamental plants. Exports of ornamentals from the Netherlands alone were worth US$ 200 million in 1987. Ornamental plants were one of the first concerns of early plant hybridisers. However, they have used less sophisticated methods than those for breeding field crops. With the development of genetic engineering, and given the economic importance, there is renewed interest. The choice of flower colour can be extended, as novelty is added, such as rare blues or purples (Mol et al. 1989). Flower colour manipulation was first reported in Germany in 1987 with petunias. There have been some changes made using antisense methods. More long term objectives will be altering flower morphology, and improving vase life. Productivity will also be improved, as with other plants, by disease and pest resistance. A Netherlands company, Florigene, is producing genetically engineered roses, carnations, chrysanthemums and gerberas, with new colours (Day 1989). Unlike foodstuffs, there will not need to be proof that they are safe for human consumption.

Other Plant Properties

Other desirable properties in crops include the development of plants that require minimum attention, a low number of cultivation operations, and developing crops that can be mechanically harvested. Orchard trees need to be bred that conform to a given space, so control of branching is another goal. The crops should all be ripe for harvesting at the same time. The characteristics of crops sent to further food processing steps after harvesting can also be altered to suit the machinery, e.g. the milling and baking qualities of wheat can be improved. A basic improvement is to increase the ratio of edible to nonedible parts in a plant, as was the basis of the changes to rice during the green revolution two decades ago.

Extending Animal Breeding

Animal Genetic Engineering

Farm animals will continue to be bred using existing methods of gene transfer and artificial insemination or embryo transfer, with help from bioengineering to improve fertility and reduce disease. However, recent developments may make gene transfer techniques important in the near future, and field testing of transgenic pigs and sheep is taking place. Genetic alteration can be used to improve weight gain, disease resistance and fertility. Historically, animal breeders have used new biotechnologies soon after their development, and there has been active research in this area. Genetic techniques are being increasingly used to alter animals used in both medical and agricultural research (Evans et al. 1986). In the past, animal breeders have had to rely on the opportune use of stud animals which show the qualities, using selected mating, by natural or artificial insemination or *in vitro* fertilisation (IVF) and embryo transfer. The new techniques for the isolation of genes, their manipulation, and transfer into other organisms of different species has meant that individual characteristics can be altered, introduced or removed from any organism. These techniques were developed both for research and for foreseen applications to technological use (Jaenich 1988).

Technology for manipulating embryos of farm animals has developed at the same time as genetic manipulation experiments in laboratory animals. The term "transgenic" was first applied to a mice strain that had foreign genes integrated into its genome (Gordon & Ruddle 1981). Much excitement was generated by the production of "supermice": large mice expressing a genetically transferred human growth hormone gene (Palmiter et al. 1982). The transfer of DNA into the male pronucleus of fertilised mammalian eggs by microinjection is one method for introducing novel DNA into the germ line, but this method results in multiple copies of DNA inserted at random sites. It has been found that regulatory sequences do aid controlled expression.

The enhanced growth of mice after transfer of a human growth hormone gene is an effect that is being repeated in other animals, most effectively in fish (Gill et al. 1985). One of the problems in injecting embryos of pig, sheep and cattle is that the cytoplasm is opaque, making the pronuclei invisible under light microscopy (unlike mice or rabbits). However, methods have been developed to overcome this, and fusion genes (mouse metallothionein promoter with human growth hormone gene) have been injected into pronuclei of rabbit, pig and sheep ova. The DNA was integrated and expressed in rabbits and pigs (Hammer et al. 1987) in several laboratories which have published similar results (Jaenisch 1988). Pigs that are being tested, were found to grow more rapidly, but have a high morbidity. The ability to produce pigs exhibiting only the beneficial side of growth hormone gene expression, increased weight gain and less fat, requires better control of gene expression, and alternatives are being pursued (Pursel et al. 1989). A deeper understanding of genetic regulation will come as more alternatives are tested. In British experiments the side-effects were absent. They have inserted the gene so that it can be turned on or off. The idea is to put a chemical trigger into the feed to control the amount of fat on these transgenic animals. There are transgenic pigs in

Adelaide, and sheep in Sydney. Researchers in Texas, USA, have produced transgenic cows with inserted human oestrogen receptor gene, insulin-like growth factor gene, and bovine growth hormone genes. The aim of all these insertions is to grow leaner, faster growing cows, and cows that produce more milk (MacKenzie 1990).

It has recently been found that it is possible to make mini-mice by genetic engineering of the growth hormone gene. Researchers, Kopchick and Chen, inserted an altered growth hormone gene into mice expecting larger mice, but found that they obtained half sized mice (Weiss 1990). The altered growth hormone may bind to growth hormone receptors without stimulating growth. It may be useful for treating people who have giantism, or disorders leading to above normal growth. It will further help elucidate the mechanism

In addition to improving growth rate a major target of genetic engineering in sheep is to improve wool production. Selective breeding has been used to improve fleece densities and wool growth. One limiting factor is nutrient and energy supply to the wool follicles (Rogers 1990). An increase in wool growth rate has been observed in genetically engineered sheep with higher levels of growth hormone. Another approach is to improve the balance of amino acids, particularly increasing sulphur amino acids, in the forage (Altenbach & Simpson 1990).

The discovery of a fertility gene factor in merino sheep is of potential use for animal breeding(Radke & Lagaris 1986). The genotype confers increased ovulation rates and large litter sizes on merino sheep, without detriment to body size or wool production. This type of gene would be of particular value in rapidly increasing any new breeding populations' size, but is also of general application to improve fertility. Other genes which may be introduced into livestock include disease-resistance genes which may have simpler physiological repercussions, but still need careful assessment on economic and environmental grounds.

The way that animals respond to new genes will only been known after experiments. Over-expression of an exogenous gene such as that for growth hormone may affect the complex processes regulating growth rate, body composition and reproductive characters in a number of ways.

There have been attempts to make chicken resistant to common viruses, by transforming developing chick embryos with genes to increase egg production, and growth rate. Salmonella resistance would help to avoid use of antibiotics, which cause problems as they are passed on to human consumers.

Fish are more easily genetically manipulated using current techniques as natural fertilisation of eggs is external, and there are numerous large eggs which makes microinjection relatively easy (Maclean et al. 1987). Development is rapid, and does not require reintroduction into the reproductive tract of a receptive female. The best results have been obtained by transferring the regulatory sequences surrounding the genes in addition to the actual genes. There are many laboratories actively working on fish genetic engineering. The genes being transferred are both mammalian and piscine. The genes are usually spliced to a strong promoter from another gene, such as the promoter of the mouse metallothionein I gene, or the promoter of the animal virus SV40. Usually about a million copies of the gene are injected per cell, as most of the DNA is degraded in the cytoplasm before reaching the small nucleus. Some genes are correctly integrated, and expressed appropriately, and some are transmittable in the germ line. Genes of immediate

usefulness that are already available are the growth hormone genes, globin genes, "antifreeze" genes, disease resistance genes and digestive enzyme genes (Maclean et al. 1987). So far many fish species have been genetically altered using this technique. About 5% of rainbow trout hatching from microinjected eggs have integrated genes. The initial projects are aimed at improving the growth rate in commercially important fish species. It will still be some time before stable, regulatable and heritable alterations of genes in other animals will be made.

Sex Selection

Of obvious commercial value is the ability to control the sex ratio of offspring in breeding populations of livestock. It has not yet been found possible to separate semen into X- and Y-bearing sperm. However, it appears that there are male-specific antigens expressed in 8-cell embryos of mice, cattle, pigs and sheep that can be identified. A high degree of success has been claimed for sex separation in bovine embryos, and it has been reported to work also for pig and sheep embryos. There is a commercial embryo sexing and splitting kit sold in Australia. Seven days after fertilisation the embryos are flushed from the cow, then a cell sample is taken from each embryo to screen for the presence of the Y-chromosome (a male). After 2-3 hours the result is known, and the desired embryo can be split (to produce twins) and reimplanted (Glasgow 1989). It should be possible to select for the presence of other genes also.

The method used in making clones of salmon by Onosato did not involve direct gene transfer (Johnstone 1983). The sperm were eradiated before fertilisation, so that the sperm's genes were destroyed, but the sperm still stimulated the eggs to complete division so allow fertilisation to occur. The fertilised eggs were treated by high pressure to prevent the formation of polar bodies, then the eggs were incubated producing a 60% hatch rate, and 90% were clones. The purpose is to increase the number of females in the farm, as a single male produces enough sperm for the fertilisation of many more females' eggs. Males can be produced by treating the hatched fry with a male hormone, so while remaining chromosomally female about 80% could function as males.

Parthenogenesis occurs when a female egg develops without incorporating any of the male chromosomes into the offspring, as is seen in many birds. This was reported to be inducible in rabbits in 1939 (Pincus 1939), but is not widely seen as a source of clones. It appears that for proper development of mammalian embryos, genes from both parents are needed, as genes are differentially used from paternal or maternal chromosomes (Monk 1988, Thomson & Solter 1988).

Embryo Splitting

The most successful type of cloning that has been reported for mammals involves the splitting of preembryos into more preembryos which can then develop into several clones. Much early work was done by Beatrice Mintz who began to manipulate mouse embryos over twenty years ago (Mintz 1967). She used an enzyme to break up the gelatinous coat of blastocysts, then mixed the cells, blastomeres, from several sources and found that the cells would aggregate. The cells of 32-cell embryos were found to be totipotent, and she reported that in the first thousand born mice there were no "monsters". The aim of these experiments

was to trace cell lineages from embryo to adult tissues. These experiments showed that embryos could be split and reformed. Blastomeres of early cleavage-stage embryos of cattle, horses, pigs, sheep and mice have resulted in normal development from as little as half or even a quarter of the normal complement of cells (Solter 1987). There have been live births of 2-4 clones. Development and the ease of manipulation may be species dependent.

A related alternative that has been used for sheep is to combine whole blastomeres (cells of a blastocyst) from 8- and 16-cell embryos with enucleated or nucleated halves of unfertilised eggs. Single egg cells were bisected, then the egg halves were fused with single blastomeres resulting in live, normal, sheep (Willadsen 1986). This type of technique is useful for agricultural breeders to rapidly increase the number of a breeding stock. Single blastomeres from 8-cell embryos can be combined with single blastomeres from 4-cell embryos, and there is a tendency for the nucleus of the 8-cell blastomere to become the genotype of the sheep. This does not make many clones, but rather groups of 5-10 clones (Willadsen 1985).

The use of embryo transfer is becoming as common as artificial insemination in agriculture, and is similar in price and success rate. Artificial insemination has been standard practice in agriculture for 30 years, and embryo transfer for several years (Womack 1987). It is possible to recover a dozen or more embryos from individual superovulated cows. There are thousands of pregnancies a year produced by embryos that have been transferred.

One major development in embryonic manipulation is the use of embryonic stem (ES) cell lines. These ES cell lines are established in culture from preimplantation blastocysts and can colonise both the somatic and germ cell lineages of chimeric animals following their injection into host blastocysts. In order to characterise the mutations in new mice a cultured totipotent cell line was needed. Cells from teratocarcinomas, tumours that arise from undifferentiated embryonic cells (Stewart & Mintz 1981, Marx 1982) can be grown as tumours in mice, but not in culture. By mixing in these cells to make chimeric mouse embryos (Hogan et al. 1986), some of the mice had these cells established as the germ line (these tumour cells did not lead to tumours in the mouse). The breakthrough was in 1981 when Evans produced the first ES cell line (Evans & Kaufman 1981). These ES cell lines can be genetically-manipulated, the desired transformed somatically growing ES cells selected, and used to make chimeric embryos which when born give rise to new strains of mice.

Environmental Applications of Microorganisms

There have been, and are many future possible uses of microorganisms in the environment, and this range has been greatly expanded by genetic engineering. The novelty of biotechnology is its ability to exploit the universality of the genetic code to combine, in a single organism, major adaptive traits developed by very different organisms. More details will be given in chapter 8 on the release of GMOs into the environment. Some of the current uses are summarised below.

* Bacteria can be used as pesticides, for example to carry the Bacillus thuringiensis

insecticidal proteins.

* Bacteria (Pseudomonas syringae) that have reduced ice-nucleating ability have been sprayed onto plants to reduce frost damage. Conversely, ice-nucleating bacteria and the ice-nucleating protein from P. syringae have been successfully tested for use in artificial snow-making.
* Viruses (Baculovirus) can also be used as pesticides.
* There are many possible uses of viral vaccines, against human diseases such as Hepatitis A, B, and C; polio, rabies, malaria; and against animal diseases such as foot and mouth disease, sheep foot rot, or tapeworms.
* Plant symbionts can be introduced, such as nitrogen fixing bacteria, which reduce the need for fertilisers. Mycorrhizal fungi can be used to increase plant growth rates by improving the efficiency of root uptake of nutrients.
* Bacteria can be used to degrade toxic compounds, such as heavy metals, organic compounds, phosphorus, ammonia or other pollutants. The first major use of bacterial degradation of an oil spill followed the Exon oil spill in Prince William Sound, Alaska in 1988. In this case, genetically modified bacteria were not added, but fertiliser to allow the low number of naturally occuring bacteria present in any soil that can degrade hydrocarbons, to multiply. The fertiliser is called Inipol. The technique is only applicable to beach areas, as the fertiliser will not cling to rock surfaces. The treated areas were dramatically improved within fifteen days, and even the underlying soil at a depth of one foot was degraded within 40-50 days. This was particularly important in the low temperature arctic environment where oil degrades very slowly. There was further areas treated in the 1990 summer, as there are large areas. The technique is not easy, but effective. It has stimulated research into this area. There has also been use of oil-degrading bacteria in the open sea in an oil tanker accident in the Gulf of Mexico in June 1990. It would be an advantage to destroy the oil before it reaches land, and also before it kills marine life.

8. Environmental Safety of GMOs

Risks from Laboratory Applications

Safety of this technology is a serious concern of many people. It has been important since the first use of genetic engineering in the early 1970's. Public awareness of all forms of genetic engineering has recently increased again with the first field trials of GMOs. The public in general have an inflated fear of genetic manipulation, which we can say in mid-1990, is largely the result of a lack of and misinformation rather than realistic fears. A voluntary moratorium on several types of genetic experiment involving use and construction of genes and their insertion into vectors for their multiplication in bacteria was imposed in the 1970's (Wheale & McNally 1988). This has long been removed as the potential hazards have been assessed and it was decided that suitable physical and biological containment should be adequate. "Biological" containment advocated the use of "crippled" host cells and vectors, such that these would have no success in colonising any environment outside that of the contained laboratory even if they managed to escape from it. Since the initial categories of physical containment were decided on there has been widespread experience gained in the practise of these experiments, which has resulted in a decrease in the assessed hazards and thus the type of containment judged necessary. The principle of biological containment is still used for most laboratory experiments, especially when dealing with human genes and/or tumour-promoting agents. Physical containment is not so strict, but is still maintained for work on tumour or disease-promoting agents.

Before the appearance of GMOs there have been harmful effects from some of the accidental releases of organisms from laboratories. In 1958 tobacco blue mould (Peronospora tabacina) was brought into the UK for a research institute. In that year the mould spread to four other institutes, including one in the Netherlands, and to a commercial tobacco crop in England. In the following year the disease appeared in the tobacco fields of Belgium and the Netherlands, from where it spread quickly across the rest of Europe (advancing in Germany at the speed of 5-20 km per week). After several years of crop breeding resistance was increased, but it is a powerful example of the risks of accidental release of new organisms (Mantegazzini 1986).

The recent release of some agriculturally important bacteria into the environment, several years after it was first planned, highlights the growing ease with which scientists now regard some types of genetic manipulation. No major problems have arisen, but registration of work and containment levels are useful requirements. Some examples of the current concerns include (Mantegazzini 1986):

* spontaneous mutations in pure and mixed cultures when growth conditions are changed

* toxins produced in thermophilic systems
* modification of viruses during fermentation
* cloning of toxic genes and the introduction of antibiotic resistance genes into microorganisms not known to naturally acquire them.

The principle problem now in all work is not mechanical, but of laboratory discipline. Safety committee's exist in all major laboratories, but there is still room for laxity. Medical surveillance of laboratory workers should be more common in case there may be long term affects of exposure.

There are no known health hazards that are specific to genetic manipulation. However, some of the organisms used, especially microorganisms, are capable of infecting humans so can present health hazards. There could be several ways in which genetic manipulation could result in hazards to humans. A GMO which facilitates delivery of a biologically active gene product to a specific tissue could occur. Autoimmune disease resulting from production of antibodies to a GMO or gene product,. Or enhanced immune response to proteins that are fusion products of the proteins that one has become immune to. In Britain, the Health and Safety Executive is trying to implement a scheme for surveillance as recommended by the U.K. Advisory Committee on Genetic Manipulation. It advises that people working with certain categories of GMO should carry cards, and also have cards attached to their medical records, that would allow contact with a supervisory medical officer should they get sick, as one way of monitoring any effects. It also recommends the storage of serum samples before conducting such work, to allow comparison at a later date in the event of illness.

There is still controversy over the use of genetic engineering in industry in some countries. A West German court ruling in November 1989 forbid the use of these techniques in industry until there is a better legal basis for regulation. This forced Hoechst AG to stop the construction of a factory for two years, until recently when a law was introduced. The application will be considered now that Germany has a gene technology law. The West German law also fits with an EEC directive on genetic engineering that provides minimum protection in EEC countries without regulations,taking effect in 1991. The German's are particularly sensitive over the use of genetics. Industrial size means that any problems could be on a larger scale, and the large number of GMOs increases the chance of release. The sterilisation of waste products is costly, but very important.

Guidelines for Contained Genetic Engineering

The European Parliament has approved a new directive to regulate both the contained use of GMOs and deliberate release. It is a useful example of simplified regulations and is one model. The points to be considered in the safety assessment include characteristics of parental and modified organisms, health considerations such as pathogenicity, and environmental considerations. There should be methods available for decontamination of areas in the event of accidental releases. There are three classes of operation, depending on the organism. The required information is laid out in the legislation in detailed form (EP 1989), and is shown in Table 9-1. Member states have eighteen months from April 1990 to implement the directives through national legislation.

Table 9-1: European Specifications for Contained GMOs (EP 1989)

Specifications	Containment Categories		
	1	2	3
Viable microorganisms must be in a system which physically separates the process from the environment	Yes	Yes	Yes
Exhausted gases from the closed system should be treated so as to:	Minimise release	Prevent release	Prevent release
Sample collection, addition of media and transfer operations to another closed system should be performed so as to:	Minimise release	Prevent release	Prevent release
Bulk culture fluids should not be removed from the closed system unless the viable microorganisms have been:	Inactivated by validated means	Inactivated by valid chemical or physical means	Inactivated by valid chemical or physical means
Seals should be designed so as to:	Minimise release	Prevent release	Prevent release
Closed systems should be located within a controlled area	Optional	Optional	Yes, purpose built
Biohazard signs should be posted	Optional	Yes	Yes
Area should be restricted to nominated personnel only	Yes, work clothing	Yes	Yes, via airlock
Personnel should wear protective clothing	Yes	Yes	A complete change
Decontamination and washing facilities provided	Yes	Yes	Yes
Personnel should shower before leaving the area	No	Optional	Yes
Effluent from sinks and drains should be collected and inactivated before release	No	Optional	Yes
The controlled area should be adequately ventilated to minimise contamination	Optional	Optional	Yes
The contained area should be maintained at an air pressure negative to the atmosphere	No	Optional	Yes
Input air and extract air to the controlled area should be HEPA filtered	No	Optional	Yes
The controlled area should be designed to contain spillage of the entire contents of the closed system	No	Optional	Yes
The controlled area should be sealable to permit fumigation	No	Optional	Yes
It must be ensured that before final disposal, waste containing living organisms or biologically active nucleic acids are:	Optionally inactivated by validated means	Inactivated by valid chemical or physical means	Inactivated by validated physical means

Many regulations are written principally in terms of microorganisms, but they need to include plant and animal cell culture also. They must also include the laboratory growth of transgenic plants and animals, and define what is contained or not. The disposal of such organisms should be performed in a similar way to microorganisms. Larger organisms do have the advantage that they are not spread as easily as microorganisms, but pollen from plants or animal insects could be potential vectors.

Field Release of GMOs

Biotechnology is advancing into areas that depend on the introduction of genetically modified organisms into the environment. At the time of writing there have been over 250 known experimental releases of GMOs (OECD 1990). There are many possible uses (Marx 1989a). The deliberate environmental introduction of any new organism, including GMOs, should be only undertaken within a framework that maintains appropriate safeguards for the protection of the environment and human health. Natural habitats already contain their own indigenous populations of organisms, organised in a delicate web of nature, which needs to be maintained.

There are several activists, such as Jeremy Rifkin, who are opposed to genetic manipulation and have tried to prevent all environmental release experiments. Their objections did mean that scientists have had to prove beyond reasonable doubt that their experiments are safe, but now that has been done, the experiments should go ahead so that we can learn from them. There have been a growing number of major reports on the release question, often with similar conclusions (NAS 1989, SCOPE 1987, OTA 1988b, Tiedje et al. 1989, HMG 1989b). There are serious ecological concerns, and ecologists stress that the organism should be evaluated and regulated according to their biological properties, such as their ability to tolerate various environments, rather than according to the method of manufacture. Not every new genetic possibility has ever been tried, so there are concerns regarding the introduction of new organisms.

The first experiments are being conducted in as closed environmental situations as possible. Our past experience with GMOs is principally in controlled situations, and we must be careful about shifting to new environments (Sharples 1987). The initial experiments on plants and animals are in enclosed research areas, but when they have proved safe and are economically useful, then they will need to be grown in large quantities. It may be feasible to use enclosed farms for some animals, especially such as fish or chicken farms, or even pigs or cattle (assuming battery farming is acceptable).

To be of a major practical use to worldwide agriculture, any GMO must be released into the environment. Only small scale agriculture can be conducted in closed environmental systems, though some important products used today are produced in that way, such as eggs from battery farming of chickens. There have been many field trials since 1984 when the Canadians field tested a transgenic plant. There is widespread public concern about the free release of recombinant organisms into the environment, and questions about how many organisms constitute a significant environmental release (Dixon 1985, Strauss 1987). The degree of care

required depends on the potential, or known, risk to the ecological balance and humans.

For plants, to be economically significant they will need to be grown over large areas, so that will mean free release on a large scale. If the food is to be grown where it is especially needed in the developing countries, both the economic situation and the social structure of small-scale peasant farmers, will mean completely free release is required. Serious problems have arisen from the unexpected results of the movement of weeds and insect pests into new environments. Some were deliberately introduced as pests into new environments, some introduced to solve one problem, but caused another (Brill 1985).

Some previous releases of organisms into new environments have proved to be beneficial, or at least harmless, but others have been deleterious. The question of environmental release of GMOs is applicable to the release of bacteria, plants, animals and humans. The possibility of a novel organism or virus being widely dispersed, and/or disruption of the ecosystem, is the main fear, and in view of the dramatic consequences possible, it is very serious. It has been considered serious enough for several countries to ban any introduction for testing already. It is a rapidly increasing problem as the technology is very cheap and becoming well known, so that many people can try different modifications. In view of the important benefits that new organisms can offer innovation should not be discouraged. A few examples are given below. A reasonably comprehensive list is produced by the OECD on a database (OECD 1990).

Degradation of Pollutants

Bacteria can be made to degrade environmental pollutants. There are a range of bacteria available that can metabolise, or literally live off substances while removing them from the environment, including many important pollutants such as polychlorinated biphenyls, dioxin, herbicides, pesticides and oil spills (OTA 1988b). The first patent obtained for a microorganism involved the engineering of Pseudomonas strains to degrade chemicals found in oil spills. The genes enabling degradation of environmental pollutants can be introduced into different bacteria. For instance the ability to degrade toluene has been transferred into bacteria that can live a zero degrees Celsius (Lindow et al. 1989). Many of the bacteria used to supply the genes are actually discovered at hazardous waste sites, after naturally evolving to cope with the chemicals present. This pollution problem is quite serious, so this could be a major use. A bacteria that can reduce the concentration of trichloroethylene by a thousand times has recently been made (Winter et al. 1989). Trichloroethylene is one of the most significant environmental pollutants, and a suspected carcinogen (cancer causing agent). The use of bacteria to reduce the level of it in drinking water could be very important.

There are other bacteria that can be used to extract and concentrate heavy metal containments from places such as land fills, mine tailings, or low grade mineral ores. There are organisms that can extract cobalt, and research to produce mercury concentrating bacteria. One study found that heterogeneous microbial populations may be better than single species systems. The organic matter needed to act as a metal-chelating biomass can be reused, with autodigestion of excess biomass. Acclimation to high levels of one metal, e.g. cadmium, did not confer acclimation to another metal, e.g. copper (Lowe & Gaudy 1989). Genetic engineering will be

needed to insert multiple genes to allow recovery of the mixture of toxicants at many sites. These metals are also valuable to recover, so the work has dual benefits. High value products, like precious metals, provided some incentive to the process, and there are commercial products available.

There are also organic pollution problems which may be treated by using bacteria, one of the most important being wastewater treatment schemes. It is also possible to use fungi for some of these applications. The fungi are attached to woodchips which can be mixed with the polluted soil, to metabolise pollutants.

Bacterial Mining

Mining operations have long benefitted from the activities of naturally occurring microbes. From 1,000 BC mine workers in the Mediterranean basin recovered the copper that was leached into mine drainage waters by bacteria. The Romans in the first century, and the Europeans in the sixteenth century used microbial leaching. However, recognition of bacterial leaching did not occur until the 1920's, and the bacteria Thiobacillus ferroxidans, which leaches metal sulphide ores, was not identified until 1947 (Woods & Rawlings 1989). Bacteria are used to extract 10-20% of the world's copper supply. In Canada, bacteria that leach uranium are also used (Lindow et al. 1989). By the year 2,000, the microbial metal industry is estimated to be worth US$ 90 billion. Bioleaching also has the potential to remove sulphur from fossil fuels, which would decrease acid rain. It is certainly more energy efficient and less polluting than smelting of low grade ores. Genetic manipulation is being investigated, but is at an early stage.

There has also been research into the use of microorganisms to enhance oil recovery. Compounds produced from microorganisms may be added to reservoirs so that crude oil viscosity is reduced and it is easy to displace. Also microorganisms themselves may be released. Some field trials have been conducted with the injection of Bacillus and Clostridium species together with fermentable brew, to produce carbon dioxide, methane or other gases. The carbon dioxide makes crude oil less viscous, and the gases in general can repressurise the reservoir for further pumping (Mantegazzini 1986).

A wide range of fungi can solubilise coal, to make a liquid product. The liquid product has potential as a chemical feedstock, and as a substrate for further microbial modification to a fuel gas (Wainwright 1990).

Nitrogen Fixation

The main type of microbial inoculant in agriculture is currently Rhizobium. Certain crops require inoculation because of the low local population of the specific Rhizobium species which are required for particular crops. There have been release experiments with R.leguminosanum with a plasmid containing a marker transposon determining resistance to the antibiotic neomycin. Root nodules have been traced for two years since release with no horizontal gene transfer observed (Hirsh 1989). The release of genetically altered nitrogen-fixing bacteria R.meliloti, designed to increase its nitrogen fixing capacity with alfalfa was another trial (Van Brunt 1987a). This may lead to higher plant growth rate, and less need for nitrogen fertiliser, saving money and alleviating nitrate pollution problems that arise from nitrogen fertiliser application.

While we have only relatively few examples of the release of GMOs into the environment, we do have much potential information on the dispersal of bacteria already. Many pathogenic bacteria are continuously released into the environment in sewage, and millions of hectares of land are inoculated with Rhizobium each year to improve the growth of leguminous crops (Behringer & Bale 1988). It is generally difficult to make predictions about the potential of a given organism to become established and to maintain high populations in a given environment.

There have been other trials of microorganisms with marker genes. In 1987 there was a release of Rhizobium containing antibiotic resistant genes in Bavaria, Germany. The purpose was to determine the survival of the bacteria (found to be very low), and to investigate gene transfer (Dickman 1987). There was major public protest over this experiment, which resulted in tough guidelines.

Ice Nucleation and Microorganisms

One famous test case in the United States concerned the experiment of Steven Lindow and co-workers in Berkeley, California, who asked the National Institutes of Health Recombinant DNA Advisory Committee (RAC) for permission to field-test a recombinant strain of Pseudomonas syringae (McCormick 1985, Van Brunt 1987a). The normal bacteria, P.syringae, is present on the leaves of many crops, and it leads to frost damage of leaves in mild frosts, because it catalyses the crystallisation of water to form ice at temperatures below -1.5°C. Annual costs of frost damage to crops in the USA is US$ 1.6 billion. A strain of P.syringae was constructed that was incapable of initiating ice formation, until the temperature dropped to about -5°C (Hirano 1985). In the absence of any ice nuclei pure water can supercool to -40°C before freezing. Frost injury in plants is proportional to the logarithm of the population size of ice-nucleating bacteria on plants at the time of freezing. The genetically modified bacteria were sprayed onto plants to provide protection against frost, by replacing the unmodified bacteria of the same species. Field trials tested if the non-nucleating strain (Ice-) will replace the normal ice-nucleating strain (Ice+), and thus prevent frost injury to plants under field conditions. The technique is applicable to many plant species, and different bacteria are being engineered. Potentially this bio-control system could save much of the economic loss caused by frost damage.

There have been many protests to prevent this research, and the field trials were delayed for several years. The first experiments began in securely protected areas, the main concern over containment is the accidental release of the organisms caused by the protesters and vandals who are attacking the research sites. Both strawberry and potato plants were involved in the first release of Pseudomonas species in 1987 (marketed under the name "Frostban") (Van Brunt 1987a). By May 1989 there had been four independent field experiments to evaluate the dispersal, environmental fate, competitiveness, the chances of the bacteria spreading into the ecosystem, and the effectiveness of the bacteria. The data suggest that the there is an extremely small likelihood of any survival of these strains outside the area of use (Suslow 1989). In these experiments, previous laboratory studies of bacterial behaviour predicted the observed environmental behaviour. Various pretests were made to determine the spread and survival of the bacteria (Lindow et al. 1988). No significant difference in the ecological behaviour of the new strains was anticipated, or found. They grew at the same growth rate both in the laboratory or when co-

inoculated on plants. They were tested on 67 different species of plant in the laboratory (Lindow & Panopoulos 1988).

There are several other possible uses of bacteria with altered ice nucleation. Ice+ bacteria could be used in the water sprayers used for artificial snow-making, and might lower costs. The bacteria could be engineered to self-destruct after use. Frozen food often contains many small ice crystals, which during storage conditions, increase crystal size. It is desirable to stabilise such ice crystals, and keep their size small. It would be possible to use viable food grade microorganisms to provide the ice nuclei. There are also research uses (Warren 1988). These bacteria are important in precipitation of rain fall, but even with the large scale industrial use of them there is a negligible risk of any influence on this (OTA 1988b).

Vaccines

There has been a recombinant Hepatitis B vaccine approved for use on human beings in most countries, since 1986. There have also been small clinical trials of other human vaccines. In diseases with costly cures, or no cure, there are often compelling ethical arguments to test vaccines in volunteers. There is research on developing vaccines for Hepatitis A, dengue haemorrhagic fever, leprosy, leishmaniasis and respiratory synctial virus, as a few examples (Bloom 1989).

Vaccines against animal disease also come in this category. Recombinant virus-based vaccines have some advantages for controlling disease (Fields et al. 1986). A single vaccine can express the antigenic determinants for more than one infectious agent, reducing the costs of administering the vaccines. Inactivated vaccines are prepared by the inactivation (e.g. with formalin) of large quantities of the virus. Attenuated vaccines are made by growing the virulent organism in an unnatural host, or under conditions such that the product will then proliferate in the natural host without causing the disease (Brown 1989). Recombinant vaccines should be safer than the attenuated vaccines as only a portion of the pathogen is expressed, so there is no danger of the virus reverting to a virulent form (Finkelstein & Silva 1989). Some safe attenuated viruses can be used for vectors for the antigens of chosen diseases. The new regulations will mean that new live vaccines are likely to be safer than the old vaccines obtained by attenuation of pathogenic viruses that were brought into use on a trial and error basis. They will have to satisfy much more stringent safety criteria before being accepted.

There was an unauthorised test of a vaccine, in an attempt to vaccinate Elm trees against Dutch Elm disease. It was conducted at Montana State University, and involved inoculation of 14 trees with a genetically engineered bacteria (Pseudomonas syringae) designed to fight the fungus that causes Dutch Elm disease. The bacteria was the product of mating a recombinant DNA modified bacteria with a strain that was not. Technically, the end product was called nonrecombinant, under the RAC rules. The researcher notified authorities, but did not wait for approval. Shortly after the trial was rejected, the trees were cut down and destroyed by the researcher. The bacteria had prevented appearance of the disease up to that stage (OTA 1988b). The real danger was the deliberate release of Dutch Elm disease, a very harmful disease, rather than the novel bacteria.

There have been several trials involving recombinant vaccines. Rabies is important worldwide, and in Europe about 1.3 million foxes are killed annually in attempts to control it, and there are 1 to 4 human deaths. Several vaccines have been

successful using vaccinia virus as vectors (Blancou et al. 1986). A large scale area (up to 435 square km) field trial of recombinant rabies vaccines occured in Belgium (OECD 1990). The vaccine was made using a vaccinia virus expressing the glycoprotein antigen of rabies virus (Bloom 1989). The results of these field trials has been a steady decline in the incidence of rabies in wild and domestic animals in the area of the field trials in Belgium. Recently this vaccine has been introduced in Belgium, and part of France, in bait to protect foxes against rabies. There has also been a field trial involving rabies virus approved in the USA, but there have been long delays with local officials about the proposed test site. There are several orally administered rabies vaccines being developed.

There are plans by the International Commission of Epizootics to immunise hundreds of millions of cattle with recombinant vaccinia expressing rinderpest antigens. There is currently an epidemic in West Africa of the cattle disease, rinderpest. This is a huge experiment, and there is bound to be adventitious infection of humans with the recombinant vaccine. Humans should be pre-immunised against vaccinia virus before this trial begins (Bloom 1989).

There has been testing of attenuated strains of Salmonella typhimurium as vaccines in Australia. Salmonella is important in sheep and cattle and poultry industries and is also a human health risk. There was initially prerelease testing in *sheep* in pens by the CSIRO. The vaccine proved effective in these trials (Davidson 1990). Tested were made to detect the bacteria in the feedlot, and also during shipping (since the sheep will be exported). There is currently a test involving less than 100 sheep underway (OECD 1990), and the project is expanding.

A rare fungus, sterile red fungus, found in Australia appears to protect plant roots that it grows in, against disease. The fungus makes the plants grow up to 40% faster, and infects most plants. It has much potential (Wood 1990). This fungus is not a GMO, but should still be considered carefully prior to free release into new ecosystems.

There are some human recombinant DNA vaccines being used. There is a recombinant AIDS vaccine being tested on twenty patients in London's Hammersmith Hospital in 1990 (Cherfas 1990). This vaccine may also be effective as a form of immune therapy, and uses virus-like particles which are like viruses but contain no viral nucleic acid. They are good delivery vehicles, and the trial will also test their efficiency. There are many groups around the world working on similar goals. The vaccine for Hepatitis B has been approved for use in most countries. Given the importance of human disease, if a vaccine is efficient, it is used widely.

Biological Pesticides

There have been many species introduced into the environment as forms of pest or weed control. Many insect parasites have been introduced, and none have been shown to have become pests themselves. The history of such releases is at least 100 years old. The strategies may rely on long term survival of the new species, as is the case with the grasshopper parasite Nosena locustae. It is being used to combat crop damage by grasshoppers, which cause US$ 400 million worth of damage annually in the USA alone (Cramer 1989).

In Britain there have been several field trials of GMOs. One series has involved baculovirus insecticides, which are viruses that only infect and kill a few species of insect. They have no effect on other types of insect or other species, and

do not pollute the environment. Naturally-occurring baculoviruses have been used during this century, and more than a dozen have been employed commercially. In a series of studies at Oxford, Bishop et al. (1988) have used many precautions in their approved field release experiments of genetically modified and genetically crippled viruses (they self destruct after a certain time period). The objective is to improve their speed of action, as they normally take several days to have an effect. This may be done by inserting toxin genes into the virus. The results of the experiments have been good. The viruses killed all the caterpillars attacking the cabbages. After killing them the virus self-destructed (both in the soil or in the caterpillars), ensuring no enduring and unpredictable side-effects. If normal viruses are used, the site can be successfully disinfected by formalin treatment. The gene for insect juvenile hormone esterase has been expressed in a baculovirus, causing feeding larvae to die (Hammock et al. 1990).

The bacteria Bacillus thuringiensis has been used for twenty years as a pest control, and is standard practice for the control of mosquitoes. The spores can be dispersed in a water mixture and distributed. There are over 400 registered formulations of B. thuringiensis in the USA. There are a number of insecticidal proteins produced, the two most important are the beta-exotoxin and the delta-endotoxin. The beta-exotoxin is effective against a wider range of insects, and has a greater soil persistence, but it may be mutagenic and it is not permitted to be used in the USA. In Europe it is used in the USSR only. The strain used to produce delta-endotoxin is usually B. thuringiensis var. kurstaki. The protoxins are laid down as crystals in the spores, and only after ingestion, when the protoxin is hydrolysed in the insect gut does the active protein form (Andrews et al. 1987). It damages the membranes of the cells lining the larval gut; the insects stop eating within minutes, and are paralysed, dying within two days (Barkay et al. 1989). There have been several insecticides released using B. thuringiensis insecticidal proteins. Many of the preparations contain live bacteria (Brown 1989). Mycogen has a product called M-One which contains a variety (var. San Diego) of the bacteria.

There is only one reported case of resistance to this protein, and it was in a limited situation. If resistance does appear then other strains can be substituted. However, B.thuringiensis does not persist well in the environment, and the spores are sensitive to UV light, so the endotoxin gene has been expressed in other bacteria, which are being field tested. This would reduce the number of applications needed. The B. thuringiensis insecticidal protein genes have been cloned into a variety of bacteria. One test case was the application by Monsanto to field-test a soil bacteria (Pseudomonas fluorescans) which has been engineered to produce this endotoxin. One species of root-colonising Pseudomonas with the toxin gene can be used to treat seeds to make them resistant to cutworm. The toxin gene has been put into an endophytic bacterium, Clavibacter xyli subspecies cynodontis, that colonizes the xylem of plants to make the plants resistant to Lepidoptera. A field trial is being conducted (Lindow et al. 1989). It has also been introduced into blue-green algae which might serve as food for mosquito larvae in ponds and streams. This is in addition to the insertions directly into the genome of higher plants.

One solution to the release of live genetically engineered bacteria is to use dead bacteria. In September 1987 the U.S. company Mycogen received U.S. patents for the invention of a process that kills bacteria while preserving their cell wall as a gelatin-like capsule which remains intact until the insect pests eat them,

only then releasing the contents such as a pesticide. Almost any product could be put in the capsules. Several genetically engineered toxins are being field tested by Mycogen and Japanese companies. This invention allowed Mycogen to be the first U.S. company to receive permission from the EPA to field test genetically engineered bacterial pesticides, in 1985 (Gaertner & Kim 1988). These are alternatives to chemical pesticides which are very damaging to the environment. The live bacteria began field tests in 1987. The MCap biopesticide delivery system may remain active for 6-7 days, which is 2-5 times longer than other biopesticides which last 1-3 days. There are large scale field tests of this pesticide, called "Mycogen Vegetable Product" (MVP) underway during 1990. Several manufacturer's are already producing MVP (Watts 1989b), and it should be commercially available very soon. Live bacteria will be more useful on fast growing plants such as lettuce, as bacteria will grow with the plant avoiding the need for reapplication. The capsules do have advantages in that they are better for transporting, and a higher concentration of insecticidal protein can be made in laboratory bacteria, compared to bacteria which have to grow in the open environment and thus spend much energy on survival with less on producing the pesticide.

The World's first commercial pesticide based on a live genetically engineered organism went on sale in Australia in March 1989. It is called "*NoGall*", and it protects stone fruits, nuts and roses from Crown Gall disease, which causes worldwide annual losses of at least US$ 150 million (Wright 1989). The "pesticide" consists of a harmless strain of the disease causing bacteria, that will live on the same leaves as, and produce an antibiotic which kills, the disease-causing strain. The gene for this antibiotic is on a plasmid, which has been engineered so it should not transfer to disease-causing bacteria to make them resistant to the antibiotic. They had an eighteen month trial prior to the commercial release. There are still some opponents to its release in Australia, and there has been a call for a review of the release guidelines. The genetic change adds nothing new to the bacteria, so it might be accepted for release in other countries. If its only ecological relationship is to the disease-causing bacteria the potential negative consequences are minimised.

Transgenic Plant Field Trials

Initially trials of genetically modified plants can occur in closed greenhouses, however many plants respond differently to conditions in a greenhouse and in the field. It is difficult in the greenhouse to simulate natural diurnal and stress conditions, and not all the plants can be grown there. Only when growing under natural conditions is it possible to determine if the genetic trait is expressed, effective, and does not have detrimental effects. Agricultural plants have been the economically most important group of exotic introduced organisms in the past. There have been a few disruptions of natural ecosystems by introduced crops. One example is the spreading of bamboo from cultivation to cover large areas of the mountain sides of Caribbean Islands.

There have been many field trials of plants containing the Bacillus thuringiensis insecticidal protein. They have shown excellent insect control, suffering no damage next to parent plants that have been totally defoliated (Delannay et al. 1989). Early market opportunities for caterpillar resistance are leafy vegetable crops, cotton and corn. Crop targets for beetle resistance are potato and cotton.

Transgenic tomatoes carrying the tobacco mosaic virus coat protein gene have

been shown to be highly resistant to virus infection, with no yield loss (Gasser & Fraley 1989). Transgenic potatoes with multiple viral resistance have been tested (Lawson et al. 1990). Many crops have been tested with resistance to viruses, another example is cantaloupe and squash with resistance to cucumber mosaic virus, papaya ringspot virus, watermelon mosaic virus and zucchini yellow mosaic virus. When we consider that the first transgenic plant was made in 1983, and there were field tests with genetically modified tomatoes and tobacco well underway in 1987, we realise how rapid progress has been. Tobacco is very easy to modify, that is why it is often use, rather than for the interests of tobacco companies. The progress is exponentially increasing.

Genetically-modified crops were tested in Europe more than anywhere else during 1989. The countries that have recorded trials of transgenic plants include Australia, Belgium, Canada, Finland, France, Ireland, Israel, Italy, Netherlands, New Zealand, Spain, Sweden, UK and USA. Plant Genetic Systems alone conducted 30 field tests in seven European countries. Their programme in 1988 involved 13 field trials, more than the total number in the USA that year. The reason for their success includes good cooperation with government agencies and independent research institutes. They have also tested crops in the USA. The Belgium-based company involves a research staff of around 100, but conducts field trials only in joint ventures (Whitmore 1989). There have been a number of field trials involving plants resistant to the Basta herbicide. There have been field trials involving genetically modified alfalfa (Medicago sativa), Brassica napus, Lycopersicum aesculentum, Oilseed rape, poplar (Populus), potato (Solanum teberosum), sugarbeet and tobacco (Nicotiana tabacum). There has been a variety of other herbicide tolerant genes tested in different plants. There have also been trials with inserted Bacillus thuringiensis insecticidal protein genes, in potato, tobacco, and tomato.

There are already many types of agriculturally important plants that have been grown with genetic modifications in field trials. The range of species is growing, and is limited principally by the ability to regenerate entire plants from genetically transformed cells. The list in mid 1990 included alfalfa, apple, Arabidopsis, asparagus, bananas, cabbage, cantaloupe, carrot, cauliflower, celery, corn, cotton, cucumber, Douglas fir, flax, horseradish, lettuce, lotus, Medicago varia, Morning Glory, Orchard grass, peas, pears, pepinos, petunias, pinetrees, poplar, potato, rape, rice, rye, soybean, squash, sugarbeet, sunflower, tobacco, tomato, trefoil, Vigna aconitifolia, walnut, white clover, and I'm sure I have probably missed some out!

Release of Animals

There has been some success in the production of faster growing fish. The work has been largely confined to fish in secure containment facilities. In mid-1989, a release system for genetically-engineered carp was approved by the U.S. Department of Agriculture (USDA) in the USA (Ezzell 1989). The carp contains trout growth hormone genes, and in the laboratory they grow significantly larger than normal carp. They were to be tested in a pond at a University in Alabama, with barriers to prevent escape to the open water. However, at the time of writing there are still delays. The USDA formal environmental assessment has been released publicly (USDA 1990), but critics of the release still oppose the outdoor pond

experiments, arguing that carp is a "weedy" species and a potential risk to other fish if it escapes. The

There have been other ways used to genetically alter fish. One technique is to use heat shock to induce triploid salmon (triploid means three copies of each chromosome, instead of the normal two copies). The result is that the salmon do not spawn, but continue to grow. There are plans to introduce them into Lake Michigan. They actually have no genetic affect on the existing salmon, as they cannot breed and pass on the abnormality. Triploid carp are being made for control of waterweeds (OTA 1988b). The advantage of these fish is that they are sterile and cannot breed, so that if there is any adverse environmental effect it may be controlled by the number of fish introduced to the ecosystem. These genetic techniques will supplement the other methods used for breeding fish.

One success has been the breeding of salmon in Norway. During the last thirteen years the salmon involved over three generations have increased size by nearly 40%. Aquaculture in 1985 produced 13% of the world's fish, and it is increasing rapidly, which may take some pressure off the falling stocks of wild fish.

A new method of controlling the blowfly is being tried in Australia. The blowfly costs sheep farmers about A$ 200 million annually. CSIRO scientists are releasing 700 million genetically manipulated blowflies during the 1990 and 1991 summers on an isolated island for field trials. A sex-linked gene translocation will cause sterility in the male line, and another mutation causes blindness in females (Ewing 1990). This type of approach is also being used in California in attempts to control Mediterranean fruit fly. Until now, insecticides have been used, but the new approach is to introduce up to 400 million sterile flies every week.

There have only been limited trials of transgenic farm animals so far, as there have not been any useful traits consistently expressed. Small closed experimental farm trials have been underway for several years in Australia and the U.K. Larger trials are expected soon, and will challenge regulators. While the animals themselves can be kept inside fences, their excrement will enter the soil, raising the improbable but not impossible prospect of gene transfer.

Persistence of GMOs

The only examples of intentional release of GMOs into the environment have been recent and are few in number. Since most GMOs only differ from the parent strain in one or a few genes, they will often behave in a similar way. It is relevant therefore to examine existing cases of the release of organisms into the environment.

Many GMOs will probably be less fit than the parent organism. Part of the reason is that they have extra DNA to carry, which will slow the reproductive rate - the excess baggage hypothesis (Lenski & Hguyen 1988). However, this is not necessarily so, and even if it was it may take many generations to pass before the introduced organism disappears due to decreased fitness if the turnover rate of populations is slow. In the first field test of an engineered soil bacterium, Pseudomonas fluorescans, with a chromosomally inserted lacZY gene marker, the population sizes of the introduced parent and transgenic organisms were identical for 30 weeks. The Pseudomonas bacteria was applied to wheat plants, and the furthermost migration of the bacteria was 18cm. No transfer was observed to

drainage areas (Drahos et al. 1988). There have even been cases where competitiveness has been enhanced with the possession of foreign DNA (Tiedje et al. 1989). An example where the recombinant strain has shown enhanced survival in the environment, was the survival of Escherichia coli with a transposon ColE1::Tn5, in a farm environment (Marshall et al. 1988). A variety of responses are also seen in plants. Some support for the idea of the intrinsic weakness of artificially bred plant varieties has come from experience with modern crops, which are often incapable of survival without human intervention. However, some crops such as potatoes, can become a weed in following crops.

Natural selection will act on all organisms, including GMOs. Genetic novelty provides the raw material on which natural selection acts (Regal 1988). Selection after the release of the GMO will tend to increase the fitness of the GMO, by reducing costs associated with novel traits. If increases in fitness occur they will probably increase the population growth rate and biological competitiveness, as well as other ecological effects. These need to be considered in risk assessment. Myxoma virus released in the UK and Australia in the 1950's to control rabbit populations evolved to become less virulent. Likewise, with GMOs natural selection will act only in a way to increase the fitness of the GMO, taking no account of human intentions.

Released microorganisms are highly likely to enter freshwater or marine environments via agricultural run-off, or faecal contamination. There are various environmental factors that affect persistence, including moisture, pH, temperature, nutrient level, sunlight and other organisms (e.g. predators) (Beringer & Bale 1988). The case of Rhizobium inoculants has provided some data. It has been found that introduced strains may not compete successfully for nodule formation with indigenous populations of Rhizobium. When indigenous Rhizobium populations in soil are high it may be necessary to use a thousand-fold number of inoculants (Lindow et al. 1989). Very little is known about the biochemical determinants of competitiveness. If there is no indigenous population, then the inoculants can establish as a complete population.

In some cases the GMOs may be intended to persist at a particular level in the environment. If the GMO is going to enter a new ecological niche, it may be safe. Those organisms used for biocontrol may need to remain in the environment at a low level in the absence of a pest outbreak. However some GMOs may be required to die out after use, like microorganisms that breakdown particular toxic wastes for emergency use. There will be a minimum inoculant population required if persistence is desired. This is also a reason why the deliberate introduction of GMOs to the environment is different to the accidental laboratory introductions that have frequently occured during the course of recombinant DNA experiments in scientific research. It has been argued that given that bacteria can rapidly grow in the environment, even if we introduced a few accidentally natural selection would determine whether they survive or not (Davis 1987, 1989). However, there is a minimum inoculation population that is required in many instances, so we can not say it is always going to be the same as the case of accidental escape of a few organisms from a laboratory. The types of organism may have very different ecological niches, also.

GMOs should be designed for safety, in addition to their function. This may mean that they include some biological containment attributes to reduce their

longevity in the ecological niche to which they are released; or which alter their ability to transmit genetic material to other organisms encountered in the habitat. At the same time the GMO must persist long enough to perform its task for which several means have been suggested. Mutations can be introduced, such as those to abolish the ability to synthesise cyclic AMP and its receptor protein, as strains of enteric bacteria with these mutations have a 50% longer generation time. A gene such as hok which encodes a 52 amino acid polypeptide that mediates a lethal collapse of the transmembrane potential, that kills a certain proportion of each generation or which can be linked to a chemical inducer, has been tested (Curtiss 1988). A plasmid vector that causes the destruction of any recipient cell could also be made. There has been successful use of self-destructive baculoviruses as mentioned earlier (Bishop et al. 1988).

Detection and subsequent elimination of organisms may be feasible if they are large, such as large animals or plants, however, insects, microorganisms or viruses may be difficult to exterminate after introduction. The detection methods used all have limits, and it may not be possible to ensure that a microorganism is eliminated, as past experience has shown (Tiedje et al. 1989). The absence of an immediate negative effect does not ensure that the effect will not ever occur, it may take time.

Transfer of Genes

To some it may be comforting that interspecific gene exchange occurs naturally, but this can also be interpreted as an argument to anticipate the spread of engineered genes to members of the natural community. Transfer of engineered genes from the GMO to other organisms may occur through hybridisation in higher organisms, or through conjugation, transduction or transformation in microorganisms. If lateral transfer occurs, an engineered gene may persist in the natural environment after the GMO is no longer present. An important unknown question is how often lateral gene transfer occurs. It occurs at a higher rate in the presence of selection pressure in the environment (Levin 1988). Among microorganisms the scientific evidence suggests that it is neither so rare that we can ignore its occurrence, nor so common that we can assume that barriers crossed by modern biotechnology are comparable to those constantly crossed in nature. Current evolutionary thought does not consider that organisms are perfectly adapted to their environment, as there are important restraints for this to occur: namely, the presence of suitable genetic variants, which is what may be introduced in GMOs. Techniques are being developed to reduce the potential for gene transfer (OTA 1988b), but there is little known outside of experience with a few laboratory species.

There are four essentials of enduring lateral gene transfer, and each component is improbable (Levy & Miller 1989):

1) the origin of an unusual genotype (to the recipient)
2) its transmission to an extraspecific cell
3) a resulting advantage to the recipient cell
4) multiplication of the recombinant to numbers that render it safe from random loss.

This scheme has often occured over the long period of evolution. Genetic engineering does increase the chances of gene transfer occuring.

If we are generating novel genetic combinations, experimental observation of organism behaviour is important. One possibility is that bacterial viruses could acquire a capacity to infect higher organisms, which may upset the extremely intricate ecological balance. However, some bacteria commonly pick up human genes naturally. The genetic barriers thought to exist between species are in fact often broken (Berry 1986), especially by viruses. The argument against genetic manipulation when we cross species barriers is weak, however, as it has been found that these barriers are broken in nature. Nature has set barriers to horizontal gene transfer in eucaryotes, but trans-species gene exchange by a process called conjugation is common among procaryotes. Another piece of evidence is that plant breeders have used comparatively crude techniques for decades to transfer genes en masse from wild species into crop plants, without adverse consequences. Traditional breeding may move the desired traits together with hundreds of other genes into a new variety. There have not been any cases of detrimental gene transfer from released organisms in the past, so there is unlikely to be problems with single, precisely engineered gene alterations, unless it is an inherent property of the gene vector to move to other organisms under field conditions.

If the trait that is being transferred is already in the environment then we will have less concern regarding its transfer, especially if the particular engineered gene is present in the system that the trial is conducted in.

Antibiotic Resistance

Some opponents of free-release of GMOs claim that natural gene transfer between Gram positive and Gram negative bacteria was never observed before genetic engineering. However, there has been a very dramatic transfer of genes, apparently naturally, in recent times. The Gram positive Streptomyces produce aminoglycoside antibodies and resistance genes, but these have been transferred to a wide range of Gram negative organisms. This type of transfer has also been observed experimentally (Hodgson 1989a, Levy & Marshall 1988, Levy & Miller 1989).

There are other antibiotic resistance determinants which have been found to be widely dispersed among different bacteria, especially the transfer of genes in transposons. There have been several specific bacterial ecosystems well studied, and these include human and animal gastrointestinal tracts. Observable gene transfer of plasmids occurs at a low frequency in the absence of selective pressure, but at a greater rate with selective pressure (Levy & Marshall 1988). The actual rate of gene transfer may be constant, but the stability may be increased with selective pressure. Resistance has been observed to be transferred between different species in these ecosystems. In animals, gene transfer in certain types of bacteria occurs more readily at 28°C than at 37°C, in faeces, so the gene transfer occured in the external environment. New bacteria can then be subsequently acquired by animals by ingestion or inhalation. Transfer of resistance traits has also been observed between human and animal (chicken, calf and pig) ecosystems.

Gene transfer has not been well studied in soils, most studies involved the inoculation of sterile soils with bacteria and observation of the transfer of marker genes. Gene transfer has been observed, as it has in natural soils containing an indigenous competing flora. Conjugation was observed at levels 10-57 fold lower than in vitro matings. It can be very difficult to measure the behaviour of organisms

in controlled systems. For example, only about 10% of soil bacteria can even be cultured in the laboratory (OTA 1988b). Gene transfer has also been observed in aquatic environments, including lake water, and in sewage. Gene transfer appears to occur in a wide range of environments, involving many kinds of bacterial hosts. If there is a high concentration of recombinant modified bacteria applied to a crop there may be an increased rate of natural gene exchange with pathogens which could lead to harmful consequences, so this should be especially monitored, but so far no problems have been reported, though it does mean carefully monitored field tests are obligatory.

To avoid the selection of new genes, it has been suggested that genes should not be linked to antibiotic resistance genes as these are steadily being selected for by the extensive use of antibiotics in man's natural environments (Levy & Marshall 1988). Kanamycin resistance markers are commonly used in the laboratory selection of transgenic plants, but, kanamycin, the antibiotic, is only used in the laboratory. Even if kanamycin resistance was transferred from plants to bacteria, it would not have any significant effect as long as kanamycin is not used for animal health treatment. The chances of the gene in the plant being transferred to bacteria is very low, and has yet to be demonstrated. However, even if the transfer from plant to bacteria were to occur at a frequency of 1 in a million (the frequency in bacteria of spontaneous mutation to kanamycin resistance) there would not be any significant effect. In soil samples, about one bacteria in 100,000 are already resistant to kanamycin (IFBC 1989).

Eucaryote/Procaryote Transfer

There has been little investigation of DNA transfer between procaryotes (bacteria, fungi, and viruses) and eucaryotes, but it was recently found that DNA can be transferred between bacteria and yeast, a eucaryote (Heinemann & Spragne 1989). It has been known that gene transmission occurs between the bacterium Agrobacterium and certain plant species, in a process mechanistically similar to bacterial conjugation. The experiments used tested both broad-host range plasmids (that can promote conjugation between Gram negative and Gram positive bacteria), and a limited range plasmid, the F plasmid of Escherichia coli. The results suggest that the plasmids could be transferred between bacteria and animal cells, and plant cells, even when the bacteria do not contain specialised tumour-inducing plasmids. This lateral gene transfer has been suggested to be an explanation for discrepancies in phylogenetic evolutionary trees. So it follows that GMOs may not be significantly different from the organisms that might arise by normal genetic exchange, they just increase the rate of genetic reorganisation. It would take a large number of transferred genes to change species characteristics dramatically. However, the possibility that bacteria can transfer genes to animal cells, needs to be investigated, with some strict precautions (Stachel & Zambryski 1989).

Crop plants vary greatly in their potential for hybridisation. At one extreme are crops which are maintained in cultivation entirely through vegetative propagation; at the other is alfalfa, an obligate outbreeder. We still do not know the origins of many crops, which originated by hybridisation. It is undesirable for crops to transfer some genes to their wild relatives, because the wild relatives could become competitive weeds.

Dispersal of Gene Vectors

Several systems have been devised for tracing the fate of genes in genetically modified bacteria in the environment (Barkey et al. 1989). The stability of different gene constructs will vary, even within the same bacterial species (Winstanley et al. 1989). Different systems used to trace microorganisms include luminescence-based techniques, with a plasmid containing the enzyme luciferase, so that luminometry can be used to trace the spread of organisms (Meiklejohn et al. 1989). Other systems are based on immunological detection of organisms (Wipat et al. 1989). These antibodies can be bound to magnetic polystyrene beads to concentrate bacteria. A recent trial monitorred the persistence of genetically engineered microorganisms using *in vitro* amplification of target DNA by the DNA polymerase chain reaction. The inserted DNA could be detected over a longer period than the detection of live genetically engineered microorganisms by plate samples. This technique has the advantage that it focuses on the gene itself, so even if the gene was transferred to other organisms it would be detected (Chaudhry et al. 1990).

The first spray releases of genetically engineered ice-nucleaion deficient Pseudomonas bacteria were monitored. The EPA Office of Research and Development designed a sampling procedure to determine the drift of the bacteria during aerosol application, and to determine the movement of GMOs. Less than 0.001% of the total viable cells released entered the aerosol cloud at the plant level, the rest were directly deposited onto the plants and soil. Of the bacteria that entered the aerosol spray, 8% drifted out of the plot into buffer zones. Between 20-35m away was the maximum drift. On subsequent days, depending on the wind movement, some resuspension from plant and soil surfaces occurred. Low numbers of bacteria were spread (Lindow & Panopoulos 1988). The best way to measure spread in terms of cost efficiency was gravity plates (open petri plates at chosen sites). Factors such as the number of bacteria applied and the wind, and equipment features such as nozzle size, have effects which are being measured to determine the minimum spreading procedure. A computer model is being developed by the EPA with the results (Seidler 1988).

The range of organisms affected by a virus may be altered in less direct ways. A laboratory study of a pathogenic plant virus showed that by altering a single gene, the range of insects that could carry it was changed. This would enable the virus to come into contact with previously unaffected plant species (HMG 1989b).

There needs to be experiments to determine the distance that pollen spreads (on insect vectors this can be over large distances), and how it hybridises. Plants often show little barriers to hybridisation, so there is always a potential for exotic pollination (Young 1989). Hybridisation has often been observed in sorghum and wild relatives, but there is still no evidence that traits such as resistance to insect pests have spread from traditional crops to wild relatives (HMG 1989b).

There has been little research conducted on cross-fertilisation; of GMOs There has been a study performed at DSIR Crop Research, New Zealand. Transgenic potatoes resistant to chlorsulfuron were grown with a border of wild type potato plants to measure pollen dispersal. The frequency of transgenic seedlings among the progeny of wild-type potatoes growing within the trial was about 1%, but only 5 in 10,000 of the progeny from wild-type potatoes planted up to 4.5m from the trial, were transgenic. There were no transgenic progeny recovered from wild-type potatoes growing 4.5 to 10m from the trial (Tynan et al.

1990). This type of study is very useful for risk assessment, though in many countries it would not have been allowed for fear of much greater spreading of pollen. However, since it has been performed, it should allay the fear of long distance pollen dispersal in potatoes, providing that the transgenic potatoes are surrounded by a suitable buffer zone of wild-type plants.

Most of the traits bred into domesticated crops by traditional breeding, such as rapid seed germination, would be detrimental to weeds. Many of the new traits will be beneficial in weeds also, such as pest resistance. Even if there is a very limited opportunity for cross-breeding, with large numbers, it is virtually inevitable that gene transfer will occur. Crops often grow in the same region as wild relatives (Ellstrand 1988).

Intrapopulation studies are constrained by the bounds of the study site, so do not serve as adequate models for interpopulation movement. The isolation distances that plant breeders use to protect their pure stock vary widely between species. The distance depends on the breeding system of the crop. For example, the isolation distances of some crops are; lettuce 10m, common bean 45m, clover 90m, cotton 400m, sunflower and watermelon 800m (Frankel & Galun 1977). There is much research currently underway to attempt to quantify this transfer.

Examples of Gene Transfer During Field Trials

There have been several examples of gene transfer occurring between different organisms. An experiment was performed to measure the fate of genetically engineered bacteria in activated sludge microcosms. Pseudomonas species carrying genes for the degradation of substituted benzoates could survive and degrade the pollutant. There was not any adverse effect noticed on the microbial populations, as this species buffered the system from pollutants. Transfer of genes in chromosomal insertions was not observed, but transfer of genes on plasmids did occur. This did not have an adverse effect because it increased the total ability of the ecosystem to cope with the presence of toxic pollutants (Dwyer et al. 1988).

The Rural Advancement Fund International issued a communique in 1989 stating that a gene had been transferred during a field trial (Krimsky 1989). The test involved a firm called Crop Genetics International, which carried out a small field trial, involving the injection of microorganisms containing the Bacillus thuringiensis insecticidal protein gene into corn plants. The company disclosed to the EPA that the gene was found in flea beetles during the tests. The explanation would be that an insect feeding on the corn plant picked up the gene, and became a vector for transferring the gene to nontarget species. There needs to be careful monitoring of gene transfer.

There have been several trials of recombinant vaccinia viruses in cattle. The transfer between inoculated animals and others was monitored. One trial was conducted at the Wallaceville Research Centre, New Zealand, with governmental approval. The vaccine was against Sindbis virus, and was shown to be infective and immunogenic for calves. It was not transmitted to uninoculated pen contact calves, even by intradermal inoculation (Wedman 1988). A contrasting field trial was that of a vaccinia-rabies recombinant vaccine, which was tested in Argentina without knowledge of the authorities. The trial was stopped when the authorities discovered it. At this time, from the samples taken, the virus was shown to have passed from vaccinated animals to all the contact animals, and at least to one human

being involved in the handling and milking of the animals. Other animals are being tested to determine the extent of spreading of the virus (Torre 1988).

The release of animals into the environment can have equal risks as with plants, as the genes may in rare instances be transferred to other species, and may be present in the environment in faeces. The examination has to include the type of genes transferred. For instance extra growth hormone genes would not be a serious risk even if introduced to other animals. The first field test involving genetically engineered fish is in a contained pond, with a series of barriers to prevent their escape to open water (Ezzell 1989). It assumes that no smaller organisms will transfer genes to the open water, though growth hormone genes are probably harmless...

Reducing Risks of Transfer

There are several types of barriers to reduce the transfer and stability of genetic information introduced into an ecosystem. Environmental barriers include the avoidance of contact, which depends on the concentration of the components of the gene transfer system in the ecosystem. In many systems, the concentration is adequate for both transduction and conjugation. Conjugal transfer is efficient between 15-37°C, and has been observed at 6°C. The observed rates of plasmid transfer from soil bacteria to Escherichia coli may be 1000 times faster at 28°C than at 37°C. Temperature and concentrations affect the gene transfer rate (Miller 1988).

The particulate matter may have a significant effect. Conjugal transfer of many plasmids is more efficient on solid surfaces than in liquids devoid of particulate matter. There are differences observed between the types of surfaces (Miller 1988). There are different ways to stabilise recombinant plasmids. They can be joined with a DNA segment that produces a partition function, surplus DNA can be removed from the plasmid, the use of transposable elements can be avoided, as well as other factors (Imanaka 1986). More research is needed to improve stability, which will reduce the risks of transfer. Organisms have entry barriers to prevent exogenous genetic material entering the cell, and some plasmids have a limited host range. However, these barriers will not halt genetic exchange. There are also barriers to the stable integration of exogenous genes in the recipient cells, such as restriction endonucleases, and incompatibility of the system. Homologous recombination could probably occur. There are further barriers to gene expression if the gene is incorporated, though the gene transfer may still have opened up further routes for subsequent gene transfer. Many of these factors need further research.

Methods are being developed to manipulate intrinsic factors so that introduced organisms have a lower probability of transferring genetic material. The genes required for transfer, such as conjugation, can be removed from the plasmid used for the gene insertion. Disabled plasmids that are not capable of detectable gene transfer can also be made. It is also possible to use self-destructive GMOs, as previously described.

ES cell lines make the creation of transgenic animals easier, and give much more control over the exact genetic change transferred to the animals. If we are concerned about the targeting of gene changes then they have definite advantages. A consequence of this is that concerns about the safety of releasing transgenic animals into the environment, because of some unforseen low probability genetic event such as viral release, would be lessened by using animals that had only single copy

insertions, the type of control which would currently require using ES cell lines. It is possible to determine the nature of genetic insertions in animals in the laboratory prior to field release, however, this is not always done and is impractical. In light of the weight given by many to fears of unsafe release, single copy insertions are desirable. The genes can be manipulated in their natural chromosomal environments, whereas the use of conventional methods for introducing DNA sequences into the germ line allows little control over the chromosomal site of integration and the number of integrated copies.

Potential Ecological Effects

Although it may not be considered by many protest groups, the most likely potential ecological effect of the release of GMOs will be to protect the environment from many harmful chemical pollutants. Overall these new genetic technologies promise much to aid world agricultural techniques. If plants were made to use fertiliser more efficiently it would mean less fertiliser would run off into rivers causing pollution, and if they were made disease resistant then less problems would arise from the poisoning of the environment by herbicides. They are cheaper and should help to solve the pollution problems caused by the current fertilisers, herbicides and insecticides.

In some cases where the ecosystem is changing due to climatic conditions, GMOs are being developed to maintain a species presence in the area, especially with the modification of trees, which may be required by many dependent insect and bird species. Rather than worrying about the inherent nature of any inter-species interchange of the genes, the major concern is safety of the GMOs and their genes on a case-by-case level to the ecosystem. Understanding ecological interactions is crucial to the planned introduction of GMOs. Most GMOs will pose minimal ecological risk. In addition to any ecological effects, we must be careful not to squander valuable genetic resources, such as important insecticidal proteins, which insects could develop resistance to, rendering some important existing uses ineffective.

Most planned introductions are likely to be agricultural, so the negative consequences probably would involve an agricultural problem. We could use a model from the affects of traditionally bred plants and domestic animals. New varieties have been introduced in the past, just as the GMOs will be. If successful the crop will be grown over a large area. Many of the traditionally bred genetic variants are chosen because they have disease or pest resistance, so they have similarities to the GMOs. If the GMO release had an impact on the natural community, the consequence would probably be a transitory disturbance of the community structure. There are, however, some examples in nature where the acquisition of a single gene can cause ecological problems, such as antibiotic resistance genes that have been acquired by bacteria, in the gastrointestinal tracts of animals.

From past mistakes we should learn the need to be cautious when applying new technology and introducing new organisms. About 10% of the exotic species introduced into Britain have become established in the wild, and about 1% have become pests (Williamson & Brown 1986). Biological pest control has risks, and a

dramatic illustration of this in Australia was the introduction of cane toads in Queensland to curb the sugar-cane beetle. Now, both the toad and the beetle are problems (Campbell 1989). New Zealand has several examples. About 80% of New Zealand weeds are introduced species, as are over 60% of its insect pests. However, while this is the total, the results of planned introductions of biological control agents is very good. Since 1874, 225 biocontrol agents have been released on 70 target species and there is no proof that any have been harmful. What this shows is that with careful evaluation and prerelease testing, new species can be safely introduced to New Zealand ecosystems. Nevertheless, we must be careful because isolated islands are more susceptible than continental areas to new species introductions (Hatchwell 1989). The only way to remove a gene that has integrated into the genome of many organisms, causing a detrimental effect, may be to attempt to destroy the organisms.

The distinction between a crop plant and a weed is very narrow. Of the 18 worst weeds in the world, only one is not used somewhere for an agricultural purpose (Williamson 1988). There are weed oats, barleys, rices, maizes, carrots etc. A similar situation exists with domestic versus wild animals that are pests. The lesson is that we must consider releases of new or GMOs carefully, taking into consideration the factors presented in Table 9-2.

The alternative which is probably more acceptable is to put into the environment only genes that we can tolerate spreading to other species. For instance if the gene for resistance to one herbicide is spread to weeds, then another could be used. One could even imagine the possible industrial sabotage of companies by the introduction of weeds that are resistant to their competitor's herbicides. There are several methods by which weeds could arise from the introduction of GMOs. One is through hybridisation with local weeds, which was mentioned previously, and which could be the most serious. There is also the low possibility that the GMO could evolve into a weed itself (Keeler 1989). This sort of risk is probably worth the large economic savings and increased crop production that is possible using herbicide resistant plants.

Bacteria can grow very rapidly, so there could be more rapid spreading of new genes among bacteria, such as in the many species found in contact with ground water. However, with alterations such as the removal of ice-nucleation proteins, serious reasons for concern have not been found so far from the recent results of preliminary field trials.

New pests could arise, as for instance in the escape of a salt-tolerant rice cultivar from cultivated fields to estuaries (Tiedje et al. 1989). It is possible for both native or exotic species with new traits to become pests. Sometimes the change in environment means that plants may become major weed problems. For example kudzu in America, where the climate is different, and it has a small competitive advantage, has over several generations spread to become a weed. Release of a genetically modified cultivar in regions which that cultivar has many wild relatives could see hybridisation between the cultivar and wild relatives. In Africa, sorghum cereal crops have hybridised with weedy relatives to produce a serious pest known as "shattercane" which can mimic the crop (Hauptli et al. 1985).

Enhancement of the effects of existing pests could occur if they hybridised with GMOs. Weeds could acquire herbicide resistance, or insect resistance, or other advantageous traits. Nontarget species might be harmed, such as insects other than

the insect pests. The genes in farm animals might be transmitted via faeces. There has been a case with a recently applied antiparasitic drug, ivermectin, which is currently applied widely to cattle, horses, sheep and pigs in many countries. It has been found to have an insecticidal effect on the larvae of a fly which normally helps break down the dung. Most of the applied drug is quickly passed in the faeces, and the high concentration of the drug kills the insect. As a consequence, dung was not decomposed quickly enough, and it killed the pasture where it accumulated (Wall & Strong 1987).

One frequently expressed concern is the potential for GMOs to displace resident species in the receiving community, particularly microbial species performing key functional roles such as nitrogen fixation or lignin decomposition. Because redundancy of function appears to be common in microbial communities, in many cases there would be little concern over microbial species replacement caused by an introduced GMO. This effect would have the result of altering the diversity of species in the environment. However, an example of this type of displacement was the introduction of the highly competitive nitrogen-fixing bacterium, Bradyrhizobium serogroup 123, into fields, which made it more difficult to introduce the more efficient but less competitive rhizobia (Moawad et al. 1984). In this case the result was harmful. Bacteria, such as Rhizobium are being manipulated to enhance nitrogen fixation in the soil. The OTA has had a study conducted to investigate whether there could be consequences for the nitrogen cycle. Their conclusion was that the chances of adverse consequences were very remote, and that normal crop rotation could produce greater changes than microbial inoculations to the patterns of nitrogen distribution (OTA 1988b).

There are many other related scenarios. The worst possible ecological impact would be to disrupt a fundamental ecosystem process, such as the cycling of a mineral or nutrient, but that seems very unlikely. One scenario that is talked of is if organisms containing the cellulase genes (which break down cellulose, a major component of wood) were released the gene could transfer to other organisms and break down trees. However, these genes are already common in the environment, as one part of the carbon cycle, but living trees are not decomposed (HMG 1989b).

There are several models for ecological relationships, but all have limits (Tiedje et al. 1989). The disruption could be on the biotic community, or on ecosystem processes. The organisms need not totally replace another organism to disrupt the ecosystem: they can coexist. The overall record of little hazards stemming from the release of products of traditional agricultural breeding does not mean it is safe to proceed with release of GMOs. Some insight can be gained from the introduction of nonnative species. Although negative effects have not been seen from the experience with GMOs accidentally released from laboratories (Davies 1987), it does not mean that this is a valid model for release of GMOs. The laboratory itself may not be a reliable environment for modelling the larger environment, as shown with past experience.

Researchers must proceed with caution in tackling some problems, such as pollution. Incomplete degradation of hazardous chemicals can lead to the production of even more toxic by-products. The microbial degradation of trichloroethylene and tetrachloroethylene produces the more toxic vinyl chloride (Tiedje et al. 1989).

Resistance to Introduced Genes

The possibility of organisms developing resistance to GMOs is very real, and can be expected. The probability of it occuring will vary, as will the significance. We should plan strategies based on the assumption that resistance will develop, at some stage, in some trial or commercial application, and have a followup strategy.

A study in Southern Italy has shown how there have been some mutations induced by the vaccine to enable Hepatitis B virus to infect children that had been vaccinated. A total of 44 people, including infants of carrier mothers, became HBsAg positive, that is positive to hepititis B surface antigen, despite passive and active immunisation against it. In one infant this led to serious disease. The virus can mutate so that it loses the determinant that the vaccine binds to, so the remainder of the virus can infect the patient (Carman et al. 1990).

There is genetic variation in the herbicide resistance that has been found to occur in nature. Multiple herbicide resistance has arisen in the wheat weed Alopecurus myosuroides after selection due to treatment with a single compound. The mechanism of resistance is not understood which should make us very cautious in the introduction of large amounts of herbicide-tolerant plants (Oxtoby & Hughes 1990). In the laboratory it is possible to isolate mutant varieties of corn or tobacco or other plants resistant to sulfonylureas and imidazolinones, often the result of a single dominant mutation. Careful management is required, and broad farming strategies should be examined.

Organisms that have new phenotypes can provide selective pressure on other organisms. The evolution of resistance to the Bacillus thuringiensis i nsecticidal protein following the introduction of these crops has been modelled. The model suggested that the presence of the insecticidal protein will be a powerful selection pressure, which could result in acquisition of resistance (Gould 1988). There is also one situation where insect pests have evolved resistance to the insecticidal protein, when seeds stored in a silo were dusted with the spores (McGaughey 1985). This has been observed several times (OTA 1988b).

Resistance to the endotoxin has never been observed in nature, despite its continued use for many years. The spores are sensitive to UV light and degrade after several days, releasing the protoxin into the environment where it is broken down. However, if it is continually present, as it would be in transgenic plants, insects have an increased chance of becoming resistant. This has been achieved in laboratory selection experiments using Indian meal moth, where the lethal dose can be increased by 250 times compared to parent strains. Lower levels of resistance have been obtained in almond moth and tobacco budworm. The mechanism of resistance has been found to be due to alteration in toxin-membrane binding (Van Rie 1990). If this did occur it would reduce the efficacy of new resistant crops, and the efficacy of current uses of the toxin, and it could also change the role that the insecticidal protein plays in the natural ecosystem.

Modelling studies have shown that the time needed to develop resistance to the toxin could be significantly extended if some unprotected crops were planted in the mixture, as this increase in genetic variation is an important factor. This is an example of efforts directed at using the toxin genes in a way so as to reduce the rate that pests evolve resistance. This would limit the selection pressure on insects for the development of resistance. The probability of pests becoming resistant could be more substantially reduced if several genes were simultaneously used in the same

plant. Combinations of insecticidal protein and protease inhibitors could be used. In a similar way, several methods of viral protection could be used to avoid viruses overcoming plant resistance. The combinations could be changed each year to ensure the pests were not able to overcome such methods, and the techniques of genetic engineering will allow this rapid breeding. During the last few years, 60% less insecticides have been used in US cotton fields in attempts to manage the selection of pests resistant to chemicals. Resistance to one variety of toxin can be countered by application of a different variety of B. thuringiensis with a variant toxin. The conclusion is that we need to employ good ecological management skills in addition to the new technology.

Optimal Procedure

In conclusion we could suggest that there are several major sequential steps that should be followed in generation of GMOs that are to be released into the environment. These include:

1) Choice of the useful gene or trait, and a suitable target organism
2) Well designed genetic alteration and expression
3) Laboratory and/or greenhouse studies
4) Small-scale field tests with extensive monitoring for gene transfer and any ecological effects, over a variety of climates and habitats
5) Step by step addition of new laboratory tested (steps 1-4) characters in each trial
6) Commercial scale release, with monitoring

9. Regulations for GMOs

It should be standard practice that all proposals to release new organisms into the environment, in every country, should be considered by some independent regulatory authority. The factors and form of the regulations are a matter of debate, and different features are found in different reports on the subject. After consideration of these we are in a better position to judge which factors should be included in regulations.

Some developed nations have regulations, but rely primarily on an expert advisory committee (Australia and the U.K.). The USA has elaborate regulations (Kingsbury 1988, OTA 1988b), and some European countries have no regulations (Ager 1988). There are some scientists who feel that the work is being over regulated because the fears are overstated (Davis 1989). While larger nations can enact and staff their own release program, it would be very costly for developing nations. Small and/or developing nations may need the aid of an international review or biosafety committee which could act on the request of the national leaders.

The actual process of genetic engineering is allowed to be pursued, subject to containment procedures, without any general limits. This idea is supported by some recent reports on the subject (OECD 1986, OSTP 1986, LRCV 1989). There are exceptions, such as work on particular pathogenic organisms, and on offensive biological weapons research. The exceptions include pathogenic organisms that have not spread to the geographic region.

In Britain, the proposing institution must complete a preliminary risk assessment themselves, from a safety committee (HSE 1989). By following a standard procedure it makes the process quicker to review, and decisions will be made within 90 days, and in some cases, such as with a GMO with a previous release, a considerably shorter time. The procedures have many similarities, but as will be evident by the end of this chapter, different countries do have different policies and procedures.

Viewing the Product Only

There have been various definitions of GMOs. One definition from the US Office of Science and Technology Policy uses the term intergeneric organism for GMO. "Intergeneric organisms are those organisms deliberately formed to contain an intergeneric combination of genetic material. Excluded are organisms that have resulted from the addition of intergeneric materials that are well-characterised and contain only non-coding regulatory regions, such as operators, promoters, origins of replication, terminators and ribosome binding regions" (OSTP 1986). This is representative of earlier approaches at defining the type of organisms that are required to be notified.

In the USA the Environmental Protection Agency (EPA) drafted new regulations in mid 1989 which do not distinguish whether the new organism is genetically modified but focus on the properties of any organism. In September, 1989, the US National Academy of Science with the National Academies of Engineering and Medicine, which form the National Research Council, published a report which stressed two themes (NAS 1989). There is no conceptual difference between altering an organism by classical breeding techniques or by gene splicing; and regulators should evaluate field tests of GMOs on the basis of the potential hazard of the product itself, rather than the molecular techniques by which they are made. This reaffirmed the existing processes, and states that the applications can be evaluated scientifically. They argue that a broad definition of GMOs would encourage the use of genetic engineering techniques, over the traditional breeding techniques. If only organisms produced by genetic engineering are reviewed, it will discourage researchers to use the new techniques. The Ecological Society of America Report (Tiedje et al. 1989) also considers that the phenotype of a transgenic organism, not the process used to produce it, is the primary consideration for regulation.

This is in contrast to the U.K. Royal Commission which considered that GMOs can not be treated simply as products (HMG 1989b). The Ecological Society of America report does note that because many novel genetic combinations can be achieved only by molecular and cellular techniques, products of these techniques might be subjected to greater scrutiny than the products of traditional techniques. Organisms with novel combinations of traits are considered more likely to play novel ecological roles than other organisms, on average. It is important to note that phenotypic changes in plants have been observed after protoplast tissue culture, which may be because of "cryptic" transposons. This "natural" gene change has produced some variants, so designed single gene changes are not especially novel events (Yang 1988).

The United States Recombinant DNA advisory board (RAC) recently redefined the term "deliberate release" as "the planned introduction of recombinant DNA-containing microorganisms, plants, or animals into the environment". The criteria adopted meant that in large scale fermentation procedures using genetically-modified bacteria, companies only need take the same steps as applicable to an unmodified organism. This is because these bacteria have been found to be safe to handle, and the judgement is based on past experimental experience. If the engineered organism duplicates the phenotype (appearance and function) and community relationships of naturally occurring organisms or those produced with conventional methods; if the novel genetic information will not be transferred to any other organism; and if the introduced genes will have no adverse effects on the environment (OTA 1988b), then it will require little review. Also in the lower risk category would be organisms produced by recombinant DNA techniques that are functionally identical to organisms that could be produced by other methods (e.g. mutagenesis and selection) which are not now subject to review, though possibly there should be some review of these organisms also. Organisms that contain no genetic material derived from a potential pathogen, or organisms identical in function to those already approved are also subject to less review.

There have been various definitions of GMOs, and the technology is changing. In most cases organisms made by conventional breeding techniques are

excluded, even though various reports (NAS 1989, Tiedje et al. 1989) consider that recombinant DNA GMOs should be considered the same as those made by traditional techniques. Both old and new technology can change. What is the most important concern is the product, however it was made. The different attributes of the product can be considered as a part of a broad risk evaluation.

Exemptions for GMOs with gene deletions?

The RAC has also exempted from review virtually all deliberate release experiments involving gene deletions within organisms. This exemption has been extended to experiments involving single nucleotide changes and gene rearrangements within a given species of microorganism (bacteria, viruses and fungi). This is because these alterations all occur naturally, and thus have already occurred in the ecosystem. If they were to present a major hazard, then we would have already seen it. This exemption for microorganisms has not been extended to experiments on plants and animals, even though microorganisms, because of their rapid reproduction and ease of dispersal, have more uncertainties attached. This means that in those cases researchers must still apply individually to the RAC for permission to conduct the experiment. This does seem a useful precaution to retain, as it requires further experience to test the possible side affects, though deletions should generally be safe.

The Biotechnology Science Coordinating Committee (BSCC), is trying to coordinate USA policy. They have issued a list of recommended exemptions (Fox 1990). It includes many organisms that are GMOs, and is a step backwards. A broad category exemption means that potential hazardous experiments may miss being reviewed. It may also lead breeders to use exempted techniques, even if they are not the best technique, to avoid regulatory control.

Another exception is the testing of new vaccines which, because it is of high medical relevance, is excluded from compulsory review in the USA. Also the Commission of Enquiry in West Germany (GB 1987), which recommended a moratorium on the release of viruses, considered the possibility of exceptions for vaccines. The benefits and risks are balanced in different countries by different people. The German report also recommended a 5 year ban on the release of genetically engineered microorganisms containing foreign genes. There have been similar proposals considered in the European Parliament. However, the approach of the Royal Commission in Britain (HMG 1989b) has been more cautious. They argue that because of ignorance we should not immediately categorise any type of release as sufficiently free of risk not to require individual scrutiny by the Committee. Each stage of the experiment should be subject to approval and licensing.

The Ecological Society of America would not recommend the complete exemption of specific organisms or traits from regulatory oversight (Tiedje et al. 1989). There is a need to minimise unnecessary regulatory burdens, but there are other ways to do this. There are some deletions that would be potentially more harmful, such as the deletion of regulatory sequences. However, the U.S. guidelines (OSTP 1986) may exempt alterations in regulatory sequences. Also once in the environment, there is a low but distinct chance that genes could be interchanged between different organisms. Recent studies that have shown that DNA can be transferred between yeast and bacteria suggests that other eucaryotes

including plants and animals may be able to transfer DNA to bacteria, and bacteria could mediate a low level of horizontal gene transfer in eucaryotes (Stachel & Zambryski 1989).

In Britain transgenic animals that "can be recalled with certainty", that are introduced to a securely fenced field but are outside strict containment, are not regarded as intentionally introduced to the environment (HSE 1989). If the animal is not native, a permit must be issued. There should be consideration to the possible interbreeding of transgenic animals with wild animals. While large animals pose very little risk in terms of gene transmission, they should still be subject to risk assessment and review prior to release. While permission may be easily granted, it still seems desirable to monitor releases by the submission of an application for release of GMOs.

Case by Case Risk Modelling

Because the different organisms can behave in very different ways, and pose different potential problems, it is generally considered preferable to use a case-by-case assessment (OTA 1988b, MOE 1988, HMG 1989b, Tiedje 1989). What then becomes important are the risk assessment methods. Our understanding of the risks presented is much greater than several years ago, but scientists can not be complacent (Sussman et al. 1988). Some opponents of field trials claim that the onus is on scientists to establish that any real risks can be managed. There are some debates on the numbers of microorganisms that constitute the term "environmental release" (Strauss 1987), but with their rapid growth rate, any number can soon multiply to fill any environmental niche offered. It is because of this that there are calls for a moratorium on such releases (Wheale & McNally 1988). It is possible to sort planned introductions into broad categories for different levels of review. There are different criteria which can be used to determine whether an application is safe.

There are methods being developed to model the potential risks (Fiksel & Covello 1986), but still they are difficult to construct and use. Risk assessment is the use of scientific data to estimate the effects of exposure to hazardous materials or conditions. Risk management is a different activity. It is the process of weighing alternatives to select the most appropriate regulatory strategy or action. It integrates the results of risk assessment of different alternatives. When examining proposals for release of GMOs on an experimental level, risk assessment is needed. The first part of risk assessment is risk identification, after which comes risk estimation (OTA 1988b). Only after the results are known can the wider release of the GMO be considered against other alternatives, the process of risk management. Benefits are part of risk management, whereas they are not part of risk assessment.

There are many examples of small groups of closely related species in which one of the group has become established in a new environment, while others have not, despite apparently equal opportunities. It is also very difficult to predict whether a species will become a pest or not. The five main criteria for evaluating environmental impact include (OTA 1988b):

* the potential for negative effects
* the survival of the organism
* the reproductive mechanism

* the transfer of genetic information
* the transport or dissemination of the organism

A procedure for estimating the risks of each organism has been developed by the Royal Commission on Environmental Pollution (HMG 1989b) which has been called "Genhaz" (Watts 1989). It is a laid out procedure to simplify and regulate the environmental assessment of each new organism. The rules will impede some research, but there are reasons to be cautious. It points out the biggest brake on the acceleration of the number of releases would be a case of serious damage caused by slack regulations, thereby justifying close examination of each case. It also recommends that carefully monitored environmental releases will make a greater contribution to safety than a moratorium (HMG 1989b). A problem is that we may not even know which experiments are particularly hazardous and may not know what the risks are until the experiment has been attempted. We can examine each previous case to assess the potential hazards (Mantegazzini 1986), but there are many experiments which have no precedents.

There are different components of the risks. The probability of each component occurring must be multiplied together to give the likelihood of harm. The components include (Mantegazzini 1986):

* incorporation of gene for hazardous trait into an organism
* chance of release into natural environment
* survival of the organism there
* multiplication of the organism in the environment
* gene exchange or dissemination
* chance that this will be harmful

If the likelihood of the occurrence of any step is zero, the final outcome will be zero, or no harm. In the case of deliberate release the components of the equation are less, but a more detailed analysis is necessary.

One model proposed for evaluating the risk of invasion by a transgenic plant is to consider positive and negative factors in an equation (Crawley 1989). The rate of increase of the transgenic plant in a given environment will be the sum of the positive factors such as the plant development rate, its seed production, survival of vegetative parts, the immigration old transgenic seed from other sites and the establishment of transgenic plants from dormant seeds, minus the negative factors such as ability for cross-species hybridisation, effects of cross-species hybridisation, effects of herbivores, fungi and plant disease and those of mutualists.

The type of scaling of risk that can be made has been discussed, and suggestions made (see esp. Tiedje et al. 1989). The difficulty with all these models is to assign values to each component in the equation. A more detailed type of categorisation is illustrated in Table 9-2, which is useful for guidance.

The level of risk can be minimised by the selection of organisms that have favourable attributes. Good choice of organism can lower any risk. The attributes of the GMO can be different to the original organisms. An example from New Zealand came from efforts to enhance the nitrogen fixing capability of a pine tree by genetically modifying a fungus that inhabited the tree. Two normally nonpathogenic microorganisms were combined, using the technique of protoplast fusion, but some of the new strains may have been pathogenic. In one case, all the tree seedlings to which the organism was applied died (Giles & Whitehead 1977). It was not clearly established that the cause of the trees dying was the new strain. However if it was,

it is fortunate that seedlings were affected. If the disease only affected mature trees, it may not have been detected in this trial, and might have been released. This example illustrates the importance of laboratory testing prior to trials.

The results of previous field trials are important in assessing the risk. While the number of these is small, analysis of risks will be dependent upon information from contained experiments, knowledge of the parent and related organisms, and an understanding of ecology and other biological principles. Only with experimentation will adequate theories of risk assessment be able to be developed (Simonsen & Levin 1988). Until there has been more field trials, each new GMO will need to be developed as outlined in the conclusion of the last chapter, gradually expanding.

It is possible to sort out planned introductions of GMOs into broad categories for which low, medium, or high levels of review are appropriate (OTA 1988b). Some of the criteria that can be used to determine whether an application is inherently safe include:

* The GMO duplicates the phenotype and community relationships of naturally occurring organisms
* The GMO will not survive or reproduce after release
* The genetic material will not be transferred to any other organism
* The gene functions will have no adverse effects on the environment
* No genetic material derived from any pathogens
* Past experience with a similar organism or GMO
* Microorganisms present more uncertainties than do macroorganisms

Public Participation

The U.K. Royal Commission argues that individuals and organisations applying for licences to carry out field trials with GMOs should have to announce their proposals through advertisements in the local press. If they want a licence to sell or supply a GMO in a commercial product they should advertise "in an appropriate national newspaper", and in the London Gazette. Members of the public can comment to the licensing authority within 30 days, and all applications will be open to the public (HMG 1989b).

In New Zealand a public notice must be placed in the newspapers of the main cities when an application is received by the committee. The public have six weeks to submit there comments to the committee (FRWP 1987). It also recommends notices in local newspapers near the proposed test site. However, the test sites do not need to be physically marked once approval is given. In Japan the test site for the first field release was required to be well protected by a boundary, and in other countries some barrier to prevent people entering the site is required. In view of the public protests this is warranted. In a sparsely populated country the best protection against such protest is to put the test in an anonymous private field. If approval is given for a field trial at all, it should not present a harm to people anyway, so there may be little need to inform the public of the site. The most critical time is during the process of assessing the proposal.

The US Department of Agriculture introduced draft guidelines which do not provide for adequate public participation. The public does want a role in the process. The draft guidelines also emphasised the protection of proprietary information so that not all details will be released to the public. It will be interesting if the final document alters this.

Table 9-2: Attributes of GMOs and Environments for Risk Evaluation (extended from that of Tiedje et al. 1989)

	Level of Consideration			
	Less			More
Attributes of Genetic Alteration				
Characterization	Full			Poor
Genetic stability	High (e.g.chromosomal)			Low
Number of genes	Gene deletion	One		Multiple
Function	None	Regulation	Only	New product
Source of Insertion	Same species		Related	Unrelated
Vector	None	Non-transmissible		Self-transmissible
Source of vector	Same species		Related	Unrelated
Vector DNA inserted	Absent		Non-functional	Functional
Monitoring of spread	Easy			Difficult
Attributes of Parent Organism (Wild-type)				
Domestication	Totally dependent	Some	Wild	Self-propagating
Ease of control	Agents available			Not known
Origin		Indigenous		Exotic
Habit	Free-living	Symbiotic		Symbiotic & Pathogenic
Pest status	No relatives pest		Relatives pest	Pest
Survival in wild	Short term		Seeds	Longterm
Geographic range	Narrow			Broad
Gene exchange in wild	None			Frequent
Turnover rate	Low			High
Mobility	Stationary			High
Phenotypic Comparison of GMO to Parent Organism				
Fitness	Reduced irreversibly		Reduced	Increased
Infectivity	Reduced			Increased
Host range	Unchanged			Shifted
Substrate resource	Unchanged			Expanded
Environmental limits	Narrowed, but not shifted			Shifted
Disease resistance	Decreased	Unchanged		Increased
Susceptability to control	Increased	Unchanged		Decreased
Expression of trait	Independent of environment			Dependent
Previous similar release	Identical	Similar		Dissimilar
Attributes of Environment				
Selection pressure	Absent			Present
Wild relatives close	Absent			Present
Vectors for dispersal	Absent		Controllable	Present
Direct ecol. involvement	None		Marginal	Key
Alternative symbionts	Absent			Present
Environmental range	Very restricted			Broad
Simulation of test	Easy			Difficult
Public access to site	None		Little control	Uncontrolled
Monitoring	Effective			Untested
Endangered species	Absent			Present
Geographically isolated	Yes			No
Important Crops in Area	Absent			Present

International Regulations

In Europe the GMOs field testing regulations vary between countries. Experiments are underway without any control in some countries, like Italy, but had been banned completely in Denmark, and in West Germany (Klingmuller 1988). European industry formed a group called the European Biotechnology Coordinating Group which has been developing its own regulations and trying to maintain a safe standard of practice (Poole et al. 1988). Their role is being replaced as government regulations become coordinated, but it is still useful to raise the consciousness over the risks of introductions.

There have been several German biotechnology companies that have decided to build new laboratories outside of Germany to avoid prohibitive local regulations, such as BASF and Bayer. The German biotechnology companies regard the laws and regulations as being very difficult. It is necessary for companies planning to produce recombinant products to seek public approval, which makes planning unpredictable. The protest movement uses scientific "experts" to formulate objections to the proposals. This had led to young scientists leaving the country if they want to work in this area (Dickson 1989b). It had also stopped much foreign investment in biotechnology in Germany. If countries have prohibitive regulations they will lose economic benefits of this industry.

The German Gene Technology Act (Gentechnikgesetz) was passed on May 11th, 1990 (GT 1990). All proposals must be published in the official gazette and in daily newspapers, and the public have one month to submit comments. A committee is established to give a report to the competent authority, within six weeks. The committee consists of fifteen members, consisting of ten scientists, and one representative from each of Unions, Industry Safety Organisations, Management, Environmental Protection, and Organisations which represent the interests of research. Among the ten scientists there should be at least six from the area of recombinant DNA, and at least two ecologists. The bill sets up a competent authority which considers the advice of the committee, and must explain if they do not follow the recommendation of the committee. The competent authority is comprised of government ministers in related portfolios, and must report within three months after public comments have been submitted. The state, rather than federal authorities, can decide who will be the competent authority for that state, but all open air experiments and commercial products must be approved by the federal health office. This state regulation of other classes of trial could lead to multiple standards within Germany.

The first proposals for release under the new framework are already under consideration, how successful they will be is another question. The first field trial since the law began on the 14th May, with the planting of 30,000 red petunias that had the red colour inserted by genetic techniques. There were still protesters. There has also been approval for the construction of industrial genetic engineering factories, which will produce human proteins using Escherichia coli K-12 strain (Dickman 1990b).

Denmark was the first country in the world to enact comprehensive legislation designed specifically to regulate genetic engineering and the production, importation

and release of GMOs. The Danish Environment and Gene Technology Act 1986, restricted genetic engineering research to classified laboratories, and prohibited deliberate release of GMOs, except for specific exemptions by the Minister for Environment. In mid 1989 after a parliamentary debate, Denmark announced that they had authorised the first field trial or transgenic plants. The plants will be sugarbeet with either tolerance to the herbicide Roundup, or resistance to a viral disease, rhizomania (Newmark 1989). As well as the safety considerations, manufacturers need to demonstrate "usefulness" or "social need" for GMO release.

There are legal directives covering the whole of the EEC. There have been several bills put forward to the European Parliament, with the Green and left parties trying to impose a moratorium on commercial release, and the right wing parties stressed economic freedom. The new directive, approved in April 1990, gives member states eighteen months to comply with guidelines (EP 1989). The European Commission laid out minimum standards for control, with options for individual countries to impose stricter laws. The wording is where regulations "effect in member states do not provide adequate protection of human health and the environment everywhere in the community", the minimum standards must be used. The regulations include details of the required information for any proposal. Most of the information will be open to the public for comment. No deliberate release shall be authorised by the authority unless it is proven and verified to have no negative impact on the environment and humans. The objective of the release must be demonstrated to be *socially desirable.* The current European proposal has an extensive list of exclusions from regulation, so is open to criticism. Any proposal for experimental release should be notified to other countries in the Community, who can comment, but not prevent the release. This should be applicable to other countries who permit the release of GMOs when the GMOs may travel across national boundaries or into international waters. The European Parliament recommends that a single-market economy means that a product approved in one EEC country should not be restricted in others. However, this does ignore the different geographical environments in Europe.

Holland enacted regulations for GMO release in March, 1990. The procedures basically follow the European Commission's suggestions. GMOs are subject to similar procedures as other new modified organisms. The public must be notified of the location of trials, as recommended by the U.K. Royal Commission. This is despite sabotage to some GMO field trials in Holland and Belgium.

In the U.K., researchers are required to notify the Health and Safety Executive (HSE) of their plans to release GMOs, and the proposals are subject to the approval of the HSE's advisory committee. They were made the agents of new legislation in 1989. All institutions, or individuals outside of institutions must notify the HSE of their work. The definition of genetic manipulation given is "the propagation of combinations of heritable material by the insertion of that material, prepared by whatever means outside a cell or organism, into a cell or organism in which it does not occur naturally, either (a) directly; or (b) into a virus, microbial plasmid or other vector system which can then be incorporated in the cell or organism." (HSE 1989).Work must be notified at least 30 days prior to intended commencement, or in the case of environmental introduction, 90 days prior to introduction. A genetic manipulation safety committee should be set up in each institute, who will prepare risk assessments of the proposed genetic manipulation.

This system is based on encouraging cooperation of scientists, and in addition the HSE provide a range of information packages to those undertaking such work, for example on how to construct safe gene vectors, and to use different types of GMOs. This information is very useful, and may be just as important as regulations themselves.

Under the new UK Environment Protection Bill, the Department of Environment will also require notification. In some cases positive consent will be required, not from the committee, but from the Secretary of State for the Environment. The first reading of this bill was criticised for a lack of mention of the subject of public notification, and for a failure to make the advisory committee a statutory body (Maddox 1990). However, the Parliamentary Committee rejected amendments to the Bill to force scientists to make public details of their proposals for field trials of GMOs. Rather the Secretary of State will decide what information will be made public regarding field trials or products containing GMOs (Watts 1990b). This is despite the fact that most information from other areas of pollution considered in this Bill will be open to the public. If researchers fail to obtain consent they will not only face destruction of any GMOs, but a maximum five years imprisonment for noncompliance. The new controls will not apply to techniques that involve only naturally occurring processes of reproduction including selective breeding techniques and *in vitro* fertilisation. They do cover the release of organisms made by any technique for the modification of any genes or other genetic material by the recombination, insertion or deletion of, or of any component parts of, that material from its previously occurring state.

The control of the release of GMOs in the USA rests with one or a number of regulatory agencies, depending on the nature of the proposed release and the type of organism (OTA 1988b). The policies of the agencies were published in 1986, and may be changing. Before any environmental release of GMOs in the USA a formal environmental assessment of the experiment must be conducted. The situation in the USA may be complicated by individual states imposing regulations in addition to federal regulations. Several states already have enacted regulations, including Hawaii, Maine and Maryland. Other states have rejected proposed bills. The concerns are that when there is existing federal legislation, if the states have extra regulations it may be duplicative and confusing. However, some local communities see the federal regulations as inadequate. Several local communities in New Jersey, Massachusetts and California, have passed ordinances preventing the dissemination of GMOs in their areas (Mossinghoff 1989). The first proposed release of ice-nucleating bacteria in Monterey, California was prevented by a local ordinance preventing the release (Bessette 1988).

The U.S. Congress is considering several draft bills designed to help simplify the procedures. One is known unofficially as the "*Biotechnology Regulation and Research Integration Act*". It would set out uniform practices for permitting deliberate release of GMOs over the next seven years. An interagency management board would be created so that the EPA, USDA and FDA officials could assist each other in review and enforcement. The bill preempts states from prohibiting experiments that have federal approval, though the states can participate in the review by submitting comments. The states may still impose their own regulations for commercial use of GMOs (Fox 1990b). However, it is too early to know which bill, and what revisions will be accepted. It is certainly better for the experimenters

to be sure of what criteria they need to meet and what data they need to present for authorization of experiments, rather than being challenged by local court cases. The lesson for other countries is to decide on good federal legislation and to settle for only one layer of regulation. In Britain, the initial assessment committee for a GMO, from the host institute, should invite the local Environmental Health Officer to join it. This allows some immediate local input, prior to central review.

In 1986 the Ministry of Agriculture, Forestry and Fisheries of the Japanese government proposed their first draft guidelines on biotechnology. There has been much work on a case-by-case level with testing in restricted and controlled test areas to avoid the spread of transgenic plants. Up to 1988 there had been no proposals to release genetically engineered microorganisms (Uchida 1988). There have been concerns expressed over the release of GMOs (Watanabe 1988). There has been more work on transgenic plants. The first field trial was approved in 1990, after a 2.1m high fence was built around the field to keep out animals and people. A committee from the Ministry of Education drafted new recombinant DNA regulations, covering contained use of GMOs and field trials in August 1990, but these will not be available for public disclosure until approved in 1991. There is still debate on whether legislation is desirable.

Canada has an Environmental Protection Act 1988, which controls biotechnology products not subject to other legislation. Biotechnology products developed for environmental application must be subject to approved field trials before commercial manufacture.

There are several different controls in Australia. There are administrative guidelines laid down. The initial committee was the Recombinant DNA Monitoring Committee (RDMC) set up in 1981, and this was replaced after 5 years by the Genetic Manipulation Advisory Committee (GMAC). This committee advises research institutes and the government (Federal and State) on safety procedures and possible genetic hazards. Scientists proposing to release new organisms are expected to comply with the RDMC's guidelines (RDMC 1985). The details are submitted to the committee with the usual type of required information, and the proposer must establish the safety of the experiment. The committee is advisory only - it can not approve the release itself (Skene 1988). There are several pieces of environmental legislation which could be applied to GMOs, and there have been reports by law reform groups on implementing a more statutory basis for the committee.

There was a 1989 report by the Victoria Law Reform Commission (LRCV 1989) that recommended specific legislation. This would be the simplest regulatory system, especially if enacted by the Federal (Commonwealth of Australia) Government. The legislation would make it mandatory for all releases of GMOs to be notified, that an environmental assessment must be conducted prior to release, public advertisements and information concerning the release would be made available for comment, and that releases would be subject to approval from the appropriate Government agencies. The existing GMAC would be used.

Regulation of the release of GMOs in New Zealand is based on the case-by-case assessment of proposals by a regulatory committee. A background paper on the New Zealand situation was published in February 1987 by the field release working party (FRWP). After circulating a draft document, public submissions were received. Most favoured the establishment of a statutory committee which

would make it obligatory for all proposals for the release of a GMO to be notified (FRWP 1987). At the time of writing, in early 1990, the committee is still without a statutory basis, but is functioning until one is established (possibly in 1990). The Interim Assessment Group (IAG) is serviced by the Ministry for the Environment. The IAG has been given regulatory control as well as performing an advisory role. All researchers in the public sector are obliged to submit all proposals to field test or release GMOs in New Zealand to the IAG for their advice. The advice is also recommended to private researchers. Their recommendations are made to the Minister for the Environment, who may pass it on to the appropriate Minister for government departments, or to the University or private company. The information contained in a proposal will be open to the public with the exception that any sensitive, potentially commercially important, information will be protected if requested.

One thing is for sure, we do need experience, which involves small scale trials, to learn more of the interchange of genetic information in different ecosystems, before launching into the technology full scale. We ought to consider ecological "boundaries", areas of limited genetic exchange as at least provisional warning signs of potential danger zones for the casual transfer of genes between species (Suzuki & Knudtson 1989). Those trials have been underway for several years, and gradually we will begin to see some of the many benefits of the technology, and see whether any negative consequences emerge. It is important that the benefits reach the farmers and the people who need them, rather than being solely a commercial gain for another technological industry.

The harsh rules in Western Europe may lead biotechnology companies to conduct field tests in countries that have liberal laws. It will be cheaper, and easier as there are less controls. Groups of scientists have visited the USSR to examine whether it is easier to conduct field trials in collaboration with Soviet scientists, in the USSR (Watts 1990a). The testing of recombinant vaccinia viruses made in the USA, in Argentina, indicates the use of countries with less regulations. It was performed without the knowledge of local authorities, and the viruses were introduced in the diplomatic baggage of UN authorities, against Argentinean law (Torres 1988). The experiment itself was not the problem, but the way it was planned and was implemented. India has recently developed their own set of recombinant DNA guidelines (Jayaraman 1990). The International Institute for Cooperation in Agriculture (IICA) is trying to encourage biotechnology in Latin America, and in 1988 distributed regulatory guidelines to avoid the "dumping" of uncontrolled genetic engineering experimentation from developed nations. The OECD is trying to formulate guidelines, which may be harmonised with EEC guidelines. The ultimate aim is to harmonise worldwide regulations. Ecological effects and geographic ranges of organisms transcend political boundaries, so it is essential to promote international coordination of risk assessment and regulation.

Applications to Release GMOs

There need to be different factors included in applications to release GMOs, and from the desirable extent of analysis, the applications can be lengthy. The various guidelines have common features, and it is desirable that greater

international agreement be reached on the information to be provided for regulatory consideration. The key elements that need to be considered include (HMG 1989b):

* identity of personnel involved (qualifications etc.)
* Objectives of release
* location of proposed release, geographic and environmental information
* descriptions of parent organism, vector, GMO (see table 1)
* description of the manipulations used to produce GMO
* arrangements for release, preparations, timing, method, decontamination
* potential environmental effects
* monitoring arrangements
* contingency plans in case of unexpected events
* results of prior local consultation and assessment

The evidence should provide convincing evidence that the proposer has carried out a thorough risk assessment of the proposed release. A handbook will be produced in Britain, based on a system for risk assessment called Genhaz, which should help to identify environmental impacts which might otherwise be overlooked.

Different committees requirements for information vary, as do their criteria for what is a GMO. Some information is open to the public, while some information that is industrially sensitive, such as that which if made public would invalidate a patent application, needs to be protected. The expertise that can deal with the release of a microorganism may be different to that required for human applications. The members of the committee need to be flexible, and to be able to seek expert consultant advice. Some examples of specific questions that need to be answered in a proposal should include:

* Genetic Characteristics of the Organism
  - Parent Organism, identification, pathogenicity, taxonomy, source, variety, capacity for gene transfer and reproductive cycle.
  - Source of the vector DNA, and properties, capacity for gene transfer.
  - Source and function of inserted DNA, similar information to that for parent organism of the GMO.
  - Genetic structure of inserted DNA (vector and gene), and method used.
  - Verification of the number of copies of the insert in the GMO, and the genetic structure if possible (laboratory results).
  - Laboratory, and researchers who modified the organism, and precautions used in laboratory handling.
  - Results of laboratory experiments on stability, and expression of trait.
  - Does the trait involve any animal suffering?
* Environmental Properties
  - Parent and donor organism's habitats and distribution.
  - Susceptability to temperature, humidity, desiccation, Ultraviolet light etc.
  - Survival of these organisms in similar conditions to field trial.
  - Does the organism produce spores, seeds or longterm survival bodies?
  - Biological processes that the organism is involved in, ecological niche.
  - Other organisms closely dependent upon this organism in the habitat, such as competitors, and symbionts.
  - Will the GMO modify the abundance of other organisms, and what are target species? Both the predicted effects, the effects of laboratory studies,

and the parent and donor organisms actions should be known.
Are there any possible consequences for human health, agricultural production, the ecosystem and pollution in that area?
What are the consequences of long persistence of the GMO?
Consequences (and probability) of gene transfer to other organisms?

* Details of proposed site
Location of the site, nature of surrounding area, facilities, ownership, proximity to farms, roads, people's houses, other crops.
Details of supervision, will there be fences, signs etc?
The contingency plans for the unexpected, such as fire, floods, animal invasion, public protests.
Production of the organism prior to release, and transport to test site.
Elimination methods after experiment, or in event of necessary termination.
Results of relevant prior field tests on same or related GMO.
Details of any target organisms, pests etc. Ecological assessment.

* Future Goals
Why is this GMO of potential benefit, and being tested?
What would the scale of larger trials be if this trial is approved and successful?
Some evaluation of the social and economic benefits of the GMO compared to viable alternatives.

In the ideal case, the application for release of a GMO should be processed swiftly. In small countries it should be possible for a committee to provide information and advice to the researchers. If they omit some information the procedure should await the necessary information. The best system is one where there is feedback between the committee and the researchers so that they can advice the proposer. They may require preliminary experiments to be done. A legalistic approach, where a proposal may be rejected if it omits some details and requires reapplication is undesirable. In many cases the people who know the most about an organism may be those doing the experiment, so they should be actively involved in the procedure.

As well as a role for public submissions, and public representation on the committee, there should be consideration of the social benefits of such a release. Much public anxiety can be averted if the decisions are made in public. Some experiments may be merely to attain information on gene transfer, which is of general value. Most will also be of potential economic benefit. Rather than only considering the short-term questions, we need to consider the long term goals and consequences of such releases. This is especially necessary before any commercial use of GMOs, but is also applicable to experimental size trials. For example, there may be little benefit seen in developing herbicide resistance to a nonbiodegradable herbicide, and in view of the potential risks of gene transfer to weeds, it may not be justifiable even as a field trial; however, we may see advantages for a crop resistant to a biodegradable herbicide which will also reduce herbicide use.

Challenges Facing Regulators

As discussed above, there are some dilemmas facing regulators, and it may be useful to summarise some of these:

* Definition of organisms that are to be included. The definition of a GMO may be ambiguous. To make it safer, all new organisms should be considered. A simple, definition of a GMO is an organism that is genetically different from the starting organism as a result of human manipulation. However, there may be too many organisms for the regulators to consider in many countries.
* Risk Evaluation is difficult, becoming simpler only after past experience. There should be a repository of test results.
* To create a favourable climate for research and economic development, excessive regulations should be avoided.
* Consistent regulation of different classes of GMOs. This is easier in a small country, but can be very difficult in a country like the USA which has different regulatory authorities responsible for different GMOs.
* The regulations should be statutory, with little room for challenge by petty court cases.
* The same agencies in the USA both fund and regulate research.
* Consistent penalties for violators need to be assigned.
* Public opinion in the local area, as well as over the whole country, needs to be considered.

Financial Liability for Damage

There is uncertainty over the actual risks of ecological or crop damage from deliberate release of GMOs. The risks can be characterised as low probability/high consequence type. As experience with GMOs grows there will be a standard of acceptable risk set by regulations, which insurers, as well as economists, will have to assess (Fleischer 1989). The average risk to the environment from products of genetic engineering may be similar for quite different kinds of products. However, the variability in risk among successive individual cases may be higher for GMOs than other products. This produces a broader risk profile (Fiskel & Covello 1986). There are various types of risk also, to health, food safety, ecosystem disruption, pollution and technology failure.

One way to put a cost to the risks is via insurance brokers. Those releasing transgenic organisms should accept product liability and insure themselves. Lloyds of London view deliberate release as an insurable proposition (Hodgson 1989a). The risk assessment procedures will require expert advice, but this has been done in other technological risks. However, we should not leave it to the market to decide such important questions. The costs of an accident are unknown. Under the new German Gene Technology Act the German federal government will assume liability on approved experiments for damages caused, up to DM160 million..

It is difficult to assess all the benefits that will come from the introduction of new organisms, though many direct benefits can be identified. The benefit needs to be considered to the nation as a whole, or the particular benefits to farmers, or a section of the community. The benefits can be assessed in monetary terms, but other factors are important. It is difficult to value parts of the environment in a monetary way.

Food Safety & Consumer Rejection

Novel Foodstuffs

At recent conferences on GMOs the concern has been switching somewhat from the environmental issues to the issue of safety of the end product for human consumption. There are worries about genetically engineered crops, and many will soon be under scrutiny in the USA for Food and Drug Administration (FDA) approval. The regulatory authorities have been slow to consider the issues of genetically modified foods, and the increasingly larger scale plantings of crops should force them to consider these issues.

The use of recombinant DNA technology should be aimed at protecting the natural environment. For this to happen, new technologies that minimise erosion, desertification, salination and reduce the use of chemicals, pesticides or drugs should be encouraged. If we consider the large amount of antibiotics given to farm animals (half the USA production is used for animals), which results in bacterial resistance to the antibiotics so that they are no longer effective for medical use, this is a much more serious problem. However, new crops must be safe, not just better than the alternatives that are accepted today.

The British Government recently approved the production of a food product containing a live GMO. The GMO in question is a genetically manipulated strain of bakers' yeast (Saccharomyces cerevisiae). The yeast is manufactured by Gistbrocades, the world's biggest yeast producer. The yeast will be used commercially at the end of this year in U.K. bakeries, and permission is being sort also in The Netherlands, France, West Germany, Portugal, Morocco, Japan and the USA. The maltose permease and maltase genes from the yeast were combined with new promoters from another strain, of the same species. There are also some short pieces of synthetic DNA, such as stop codons, included (Aldhous 1990). The genes will be constitutive, that is, continually active, rather than inducible only in the presence of maltose and absence of glucose. The yeast should take up and digest maltose more efficiently, making bread rise more quickly. The product will not be required to carry a label indicating it was made using genetic manipulation. It has taken four years from development to approval.

Another example that may soon be approved is the use of genetically modified yeast for beer production. In late 1986, a USA Company, BioTechnia, arranged for trials at a UK Brewery for the production of low calorie beer. The yeast, Saccharomyces uvarum, contains a gene from Asperigillus niger for glucoamylase (Palca 1986). This allows faster brewing, and the beer requires no additives to remove starch as the alternatives require. If the unpasteurised beer was provided, it would contain live yeast.

It is expected that approval for limited trial human consumption of a genetically engineered tomato produced by ICI, will be given during 1990 by British authorities. It will be longer before approval is given for general public consumption. There have been taste trials of genetically modified crops in many laboratories around the world, and most scientists would be happy to eat such foodstuffs themselves, as there is no substantial difference compared to crops bred

by traditional methods. It should be one of the first plant crops to be approved for human consumption.

Plants that are genetically modified may need some preliminary testing to ensure that no secondary toxic product has been produced after the manipulation, as it has been found that some plant defenses against pesticides involve the synthesis of carcinogens, cancer-causing agents. These plants may need approval before being sold for human consumption. There are concerns that there could be harms from high levels of some toxins, which are probably of low risk, but there was the case in the 1960's over a new strain of potato called "lenape" which had high levels of a usually trace level toxin, solanine, and caused illness after eating. The range of solanine in potatoes varies 40 fold. There are unknown affects on people's allergies. The concerns also cover grains or food that can be given to animals as feed (Wickelgren 1989), though the effect of any toxin is unlikely to be passed on. There is the potential to make more nutritious plants, such as by increasing the level of the amino acid methionine in soyabeans.

There are some products that have a history of previous use. The B.thuringiensis insecticidal protein gene has been incorporated into plants for insect resistance. This protein has been licensed in various formulations since 1962 (OTA 1988b). It is available in a number of formulations in over 400 products in the USA. There have been very few instances of harm being noted, even though hundreds of thousands of tons of the protein have been administered. One harmful effect observed was an association with corneal ulcers in humans (Samples & Buettner 1983). It will be important to clarify this before approving the consumption of transgenic plants that contain this toxin.

In many European countries, if novel food proteins are regarded legally as food, they are not subject to special legislative approval. They are different to food additives which require safety appraisal. The term novel food protein can include sources of protein not previously exploited for human consumption, including novel enzymes from GMOs (Mantegazzini 1986). There does need to be further regulatory control of food proteins in this category, as it can include novel toxins. The volume of protein consumed will be much greater than if the substances were just food additives. To observe any effects due to minor constituents of food may take a considerable length of monitoring following consumption.

There have been many natural toxic substances described in plants, including existing food crops. Some act in subtle ways, such as alkaloids and teratogens, which can cause birth defects (Cheeke & Shall 1985). The actual number of naturally occurring toxicants detected in a major survey of plants was 148, with 14 found in normal diets (IFBC 1989). Compared to the huge number of food constituents, this is very small. Many substances are yet to be described. For example, some kinds of beans need cooking to make them safe to eat, and potatoes and rhubarb have poisonous parts which we need to know about to avoid eating. Some cases should be easier to predict. For example transgenic plants expressing the TMV coat protein gene are found to have 0.01% - 0.5% capsid protein per total protein. This is well below the levels found in plants infected with this endemic virus. This should facilitate registration and commercialisation of the virus-resistant plants (Gasser & Fraley 1989). It is likely that virus-resistant plants will be among the first to be approved for human consumption, however it is very difficult to predict what regulatory authorities will do with new foodstuffs.

In 1988, the *International Food Biotechnology Council* (IFBC 1989) was formed with the aim of identifying the issues and assembling a set of scientific criteria to evaluate the safety of food derived from plants and microorganisms resulting from the applications of biotechnology. They did not consider animal foodstuffs. The membership of the Council is comprised of approximately 30 companies, who set up committees to look at scientific, legal/regulatory and policy/public relations aspects.

They discuss the variability of composition inherent in foods and food ingredients, such as the nutrients and toxicants. There are several vitamins (A & D), certain trace minerals (Fluorine, Iodine, Copper, Selenium) and other essential nutrients that are consumed safely only within a narrow range. Intake below that range results in deficiency or disease, and above that range in toxicity. There are many food toxicants that are already accepted at low levels in foods. For intentional introductions a safety factor of 100 is commonly used. They surveyed the range of toxicants and nutrients in traditional foods as a basis for comparison with new foods, and as the standard for defining food that is considered safe.

They recommend that the regulation of food from GMOs be directly patterned on the existing law. This is also the recommendation of the Victorian Law Reform Commission (LRCV 1989). There are existing legal requirements for food safety which can be used (OSTP 1986). Also the possibilities of financial liability and legal suits in the USA will make companies very cautious. If the purpose of the modification is to introduce as an expression product of the transferred gene, a functional chemical entity that, if introduced exogenously, would be regulated in the GMO as a food additive or GRAS substance, then the new food would be treated as such. They proposed decision trees for evaluating the relative safety of food derived from GMOs (IFBC 1989).

The IFBC recommend that the following types of genetic elements be considered acceptable for use in food:

* Uncharacterised genetic material presently consumed in food, that was introduced from non-food species used as sources of genetic variation in developing and improving foods using traditional methods of genetic modification and for which documentation of safe food product is available.
* Fully characterised genetic material derived from nontoxic, nonpathogenic microorganisms that are not intentionally consumed as food but are commonly found in or on food and accordingly have an established record of safe use.
* Fully characterised noncoding DNA from sources that are not traditional foods. Since noncoding DNA can not encode any protein then only the intrinsic properties need be considered. The only concern is a quantitative one: large quantities of nucleic acids can cause gout.
* Coding DNA from nonfood species that have already been used as sources of genetic variation in developing and improving foods using traditional methods of genetic modification and for which documentation of safe food product use is available.

There is some possibility of secondary metabolic effects from the inserted genes. There will probably be no pleiotrophic effects as the biochemical mode of action of each gene to be inserted is known. However, because there are many metabolic routes inside cells, the excesses or absence of different chemicals caused by the inserted genes, may have effects in what is called secondary metabolism. For

example the herbicide tolerant plants often involve the synthesis of some amino acids, and there may be secondary effects, that are difficult to predict. The control of the metabolic pathways is still poorly understood, and the only way to determine them is to analyse the products of such plants.

If plants are made in a more uncontrolled many, by insertional mutagenesis there may be further unknown effects. Pieces of DNA important for regulation of different genes may be either turned off or turned on, and this may affect other genes. Because there are some natural toxins in most plants at low level, it is important to ensure that these toxins remain only at low level and are not accidentally increased in a new variety.

Alternative research is being performed at Dental Research centres in the USA. The bacteria responsible for tooth decay are being genetically manipulated so that they do not produce acids that causes the tooth decay. The new strain could be applied in toothpaste, or it could be applied once for life if competitive with other mouth bacteria (Goel 1989). This will pose interesting regulatory problems, as it will involve the continual exposure of users to the bacteria.

There are less toxins known to be present in animal foods, but care must also be taken. The tolerance for vitamins can vary, for example the level of Vitamin A in polar bear liver is 500 times higher than found in cat liver, and some dogs have been poisoned from eating polar bear liver. It is unlikely that such differences will be found between two varieiteies of the same animal, but monitorring is essential. There was recently a controversy in Australia regarding accusations that 53 genetically altered pigs were sold for human consumption without proper approval. The pigs came from a company, Metrotec, associated with the University of Adelaide. They have been trying to breed leaner pigs since 1982. The work involves pigs with inserted growth hormone genes. In 1988, Metrotec transported 53 pigs, who were the offspring of a genetically altered pig but did not express the growth hormone gene, to the abatoir. They had been given permission by the South Australia Health Commission and the National Health and Medical Research Council, as they did not express the hormone (Anderson 1990). One would not envisage any harm from consumption of these pigs.

One of the key legal points is whether the gene should be regarded as a food additive or not. When naturally occuring food is altered, there are two broad classes. In the USA, Federal Food, Drug, and Cosmetic Act, the clauses for the two classes read "in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health"; and "a food shall be deemed to be adulterated if it bears or contains any added poisonous or added deleterious substance". There are five categories of added substance that are listed, including unavoidable by-products of food manufacturing, pesticides, food and colour additives and new animal drugs (Jones 1989). The added gene will be physically made in the same way as the rest of the DNA, so is not an added substance in that sense. However, the information contained in the gene is an added substance in that reading of the definition. In the case of animal gene transfer in the USA the exclusion for animal drugs may be applied to transferred genes. However, as discussed here, and in length in the IFBC Report, most transgenic crops should present no health risk and should be approved without considering the new gene products as manmade substances, such as pesticides.

Public Acceptance of New Foodstuffs

It is important to confirm that the products used are not only harmless to the animals but are harmless to human consumers, unlike the case of anabolic steroids which have been used to increase animal growth rate but remain in the meat possibly affecting human consumers, a reason why EEC countries ban the import of such meat from the USA. There have been earlier cases with more widespread use of steroids. In Italy in 1980 it was found that diethylstilboestrol, which enhances the growth of calves was present in the veal to be used for baby food, causing infant cancers and the onset of secondary sexual characteristics (Wheale & McNally 1988).

There have been some controversial results of treating animals with recombinant bovine somatotropin (BST), as it can increase the milk yield (claimed to be about 10-20%) with improved feed-conversion efficiency without any sign of changes in meat composition. It also results in leaner lambs and pigs, which means healthier meat, as it alters the metabolism in favour of net protein gain (Lamming 1988). BST is the first product of genetic engineering to be offered to farmers. It has been approved in the USA by the FDA as presenting no risks to human health (Sun 1989), but they are still considering whether it is harmful to cows and should decide in early 1991. It will probably be rejected in Europe. The decision will be taken in late 1990. Many small farmers and the Green party do not want to use BST, and there is an immediate question of why it is needed when there has been considerable money spent to control the overproduction of milk already. In several studies using BST the cows have shown increased mastitis and stress, increased incidence of infectious diseases, reduced fertility and heat intolerance; which make it easier for large scale farmers who have cheaper veterinary help (MacKenzie 1989).

There has also not been adequate food testing performed on the milk produced from cows treated with BST. One of the BST proteins contains an additional nine amino acids compared to the normal protein. There are legitimate concerns over the safety of it. The research was dominated by the industrial companies, and they have not disclosed much information from their tests. The US Animal Health Institute is supporting the use of BST, but has failed to mention a wide range of adverse effects in about half the trials that have been conducted (Epstein 1989). Stressed cows produce more adrenalin and other steroids, which may be present in the milk or meat. Insulin-like growth factor-1, a hormone that affects postnatal growth in humans is found in BST milk, and the total level of BSTs is 50% higher than in normal cows' milk. BST is known to be biologically active in a wide range of species, including goats, sheep, pigs, mice and fish. There have been studies showing that partially-digested BST is biologically active in humans, inducing nitrogen retention. Nitrogen retention has been linked with abnormalities in the human central nervous system. Until further studies are done, industry can not say that BST is inactive in humans (Epstein 1989, MacKenzie 1989). This test case has certainly not been handled well by the agencies concerned.

Even if BST is safe, the consumer objection to milk produced may be considered enough to warrant a ban in Europe. The European Court ruled that consumer objection was sufficient reason to ban the use of steroids to fatten meat animals, so it may do the same with BST. In the USA there is also consumer rejection of BST-milk, and requirements that milk be labelled if it is used. It should certainly be necessary to label products made using BST treated animals, and the public can then be involved in the decisions regarding the use of it. A survey of

California milk producers in late 1987 indicated that many farmers would not use BST, or would wait to see the results. Their concerns were whether there would be negative consumer reaction, as well as the effects on the cows health. Some creameries will not accept BST-milk (Zepeda 1989). This consumer pressure which has resulted in bans on BST milk in some U.S. states (e.g. Wisconsin), and in Europe, is a much broader issue. More than milk is at stake, rather the way that decisions on future agriculture are made. Even if BST has no effect on humans, it may still be banned.

Consumer objection has delayed the introduction of the technology of food irradiation (Murray 1990). Irradiated food has been tested widely and found that if radiation levels are controlled it is safe. It has the significant advantage that it sterilises food, which means the food lasts longer, and it may lower the rate of food poisoning. It has been supported by the World Health Organisation for a decade, but consumer groups have opposed it, in the UK and in New Zealand. It is legal in Holland, Belgium and France, and will only be used for up to 5% of the food. There is currently much public objection to it in the UK as the government debates a bill to allow it (Coghlan 1990).

In the recent public opinion survey towards genetic engineering performed in New Zealand, the issue of public acceptance of foodstuffs produced by GMOs was addressed (Couchman & Fink-Jensen 1990). Not only is food safety an issue but as stated the consumer opinion can be influential. About 75% of the public were aware that GMOs could be used to produce food and medicines. All the respondents were asked the question "If any of the following were to be produced from GMOs, would you have any concerns about eating them?". If the respondents said they had concerns, they were asked what concerns they would have. Some of the results are presented in Tables 9-3 and 9-4.

Table 9-3: Concern expressed by the general public about using various products produced with, or from, GMOs (%) (Couchman & Fink-Jensen 1990)

Responses(%)	Types of Foodstuffs or Products:			
	Dairy Food	Vegetables	Meat	Medicines
Concerned	42.8	38.4	48.3	34.1
Not concerned	57.2	61.6	51.7	65.9
Reasons for concern	% who included as reasons:			
Unnatural	26	32	27	14
Unknown effects	22	20	21	23
Not sure what eating	14	12	15	10
Product safety	12	10	9	15
Need information	11	10	9	12
Side effects	7	5	5	12
Unknown area	4	4	4	5
Disease causing	3	2	3	1
Product quality	3	4	4	1
Animal cruelty	1	0	5	1
Anti-medicine	-	-	-	7
Don't know	11	11	12	14

The lowest level of concern was for medicines, and the highest was for meat. Of the people who had general worries about genetic engineering, the highest proportion had concerns about meat, and lowest about vegetables that were genetically modified. Of those who expressed concern about using each type of product, about half had no worries about genetic engineering in general. There was greater worry about all types of products by women than men. The level of concern generally increased with age. Therefore there may be special concerns about food made by GMOs. The most frequent reason for concern was that it was unnatural, or that it might have unknown effects, and they would not know what they were eating. This may be an important feeling to overcome, though it should be remembered that at least half the people were not concerned. This concern was shared by farmers. Scientists were more concerned about product safety.

Table 9-4: The concerns over products made using GMOs by different sectors of the New Zealand public (Couchman & Fink-Jensen 1990). The survey of the public was face-to-face, the rest were written questionnaires. The total number of respondents were; public 2034, biology teachers 277, farmers 200, scientists 258.

Type of Foodstuff or Product using GMOs:	Occupation of Respondents			
	Public	Teachers	Farmers	Scientists
Dairy Products				
Concerned	42.8	13.0	41.0	24.0
Not concerned	57.2	87.0	59.0	76.0
Vegetables				
Concerned	38.4	9.7	30.5	21.7
Not concerned	61.6	90.3	69.5	78.3
Meat				
Concerned	48.3	13.7	26.0	24.4
Not concerned	51.7	86.3	74.0	75.6
Medicines				
Concerned	34.1	9.7	29.0	19.8
Not concerned	65.9	90.3	71.0	80.2

People's awareness of food made using biotechnology such as biosweetener, biowine, and biovegetables was also surveyed in the Japanese science magazine *Newton* (1989), that was refered to in chapter 3. Some were worried, though most did not understand why it might be dangerous. 23% thought it was good to use sweetener made in bioreactors, 23% did not care, but 41% were unsure and 5% worried. With wine made using cell fusion, 28% thought it was good, 30% did not care but 30% were unsure and 3% worried. 83% knew new vegetables are being made by cell culture. 38% thought it was good, but 34% were a little unsure and 5% were worried about this. By law, food made using biotechnology is treated the same as other food; 35% thought it was no problem to treat it the same if it was safe.

Many people think it is useful to have biomedicine or biodetergent. 46% thought that it was good that medicine made by genetic recombination might be sold

soon, but 33% were a little worried, with 3% worried. Another question pointed out that recently the size of washing machine detergent packets had became smaller. 74% knew that this was because they use stronger enzymes made using biotechnology. 45% thought this was good, 21% did not care but 25% were a little worried, and 4% worried. In response to the comment that "biotechnology is starting to be used for daily life"; 55% thought that this is good, 34% were a little worried and 5% were worried.

The readership of this magazine are people with some interest in science in general, and are on average more educated than the general public. In Japan the prefix "bio-" is used to attract the public to new products, made using biotechnology. In this sense the public may be attracted by new products seen to be better. The general public may not be aware of the concerns about these products. In the American OTA survey it was found that education did not correlate with degree of concern about biotechnology, but in the New Zealand survey there was some correlation; the more educated may be aware of more risks even though they may not reject the products because they are seen to be "unnatural". Further study of this will highlight the way education may be used to inform people of the actual similarity of food made using any technique, there is far more variation among different foodstuffs that people eat. 48% of the New Zealand school biology teachers thought that the material available for the teaching of genetics and genetic engineering was unsatisfactory. This must be improved.

Better Products?

Preparations of bacterially produced "human" insulin have been available since the early 1980's. They were assumed to be better than porcine insulin, and most diabetics in Britain have been switched to the human insulin. However, there are serious doubts whether it is actually any better. One of the concerns over porcine insulin was that a few people develop allergies to it, but it is also possible to develop an allergy to the preparations of human insulin. It has been observed that those people using "human" insulin do not receive symptoms of hypoglycemia (a low blood sugar level) as they do if they use porcine insulin, which can have serious consequences. The reason for the widespread switching was commercial promotion of a new product, not necessarily a better one. There are now 17 different brands of human insulin sold in Britain, yet there has been no clinical advantage found (Lesser 1989).

Tissue plasminogen activator (TPA) is a recombinant DNA product that was developed by Genentech, as a blood clot dissolving agent. The 1989 sales were worth US$ 200 million. The U.S. Government decided that TPA was too expensive for the Medicare scheme, in 1988. A recent study has found that TPA may be no more effective than streptokinase, which is one tenth of the price, and used in Europe (Gershon 1990b). Streptokinase is derived from streptococcal bacteria, and commands a two thirds share of the market for these agents in the USA. In view of the results of this study, it will reduce the proportion of the market that TPA hoped to fill.

Protein pharmaceuticals produced by recombinant DNA technology require approval. Part of this process is the purity analysis of the product. Analytical methods have improved as the technique develops. The approval of any pharmaceutical relies upon a convincing demonstration by the manufacturer of the

safety and efficacy of the product. Before human trials, analysis must be made. There are a variety of impurities that are possible, including endotoxin, host cell and media proteins, monoclonal antibodies, DNA, and infectious agents. Contaminants can be the same substances accidentally present. Impurities can have immunological and/or biological effects (Anicetti et al. 1989). Testing is also required during the production of each batch. For example, there are approximately 750 separate tests performed in the production of human growth hormone. Recombinant DNA techniques combined with new purification methods have produced the highest purity proteins that have ever been available for human therapeutic applications (Davies 1988). Some proteins, such as human albumen, may be made using this technology because of the purity possible, and there is no risk of virus transmission, as there is with blood products.

In August 1990 the controversy over the safety of products produced by recombinant DNA technology resurfaced with the association between a batch of the amino acid tryptophan produced by Showa Denko, a large Japanese chemical company, and a disease called eosinophilia-myalgia syndrome (EMS). Tryptophan is part of a dietary supplement used to treat insomnia, depression or premenstrual tension. The outbreak of EMS in USA during 1989 led to 27 deaths, and can be traced to a particular batch of this amino acid. The batches concerned were made with lower amounts of carbon which was used to filter out contaminants, and were made using a new strain of bacteria. The actual cause has not been determined, but opponents of genetic engineering are calling for a moratorium on the approval of further products of genetic engineering. The probable cause of the EMS is a contaminant, so rather than the genetic modification being responsible, the purification procedure was to blame.

The range of products that can be produced include vaccines, hormones, and genetic probes for genetic screening. The quality of the products is regulated according to their intended use, not their method of manufacture. There are existing laws to ensure safety, and quality of these products. In the USA the FDA has a Biological Response Modifiers Advisory Committee, which assesses the results of clinical trials of new drugs. There needs to be clear evidence of a therapeutic effect, with no harmful effects, before a drug will be permitted to be more widely used. In the case of a longterm disease, the therapeutic effect may be difficult to assess, but this problem existed before the advent of drugs or proteins made using recombinant DNA techniques. The regulators must attempt to introduce useful drugs as sson as possible, in cases where there is no alternative therapy. Some proteins must be used very carefully, by experienced clinical teams, but the drug should still be approved if the criteria of use is restricted to use by such clinics.

The list of approved products is expanding. According to the 1990 annual survey by the U.S. Pharmaceutical Manufacturers Association, there are 104 different genetically engineered medicines being tested in human clinical trials or being reviewed by the FDA. About half are for cancer related conditions, and 15 are being tested for treating HIV or AIDS related conditions. Of the 104 drugs, only 11 have so far been approved by the FDA for physicians to prescribe. At the time of writing another 18 have completed clinical trials, and 14 more are in the final stages of human trials.

10. Commercialisation

The total value of world sales in 1987 of genetic engineering products was about US$ 700 million, in 1989 the annual value was estimated to be US$ 1 billion, and by the year 1993 the value should be over US$ 3 billion (Gupta 1989). This compares to a total annual pharmaceutical market of US$ 1000 billion. The world market for seeds and agrochemicals is about US$ 70 billion. Genetic engineering should take a large share of these markets. Biotechnology is expected by some, to contribute US$ 12 billion per year to seed production by the year 2,000, and US$ 50 billion to agriculture (Fowler et al. 1988). The biotechnology industry itself, is much broader than genetic engineering, and the 1983 sales were estimated to be worth US$ 15 billion worldwide. There are different estimates, but they all involve large sums of money.

Biotechnology Companies

There are many biotechnology companies established, for instance at the beginning of 1989 there were more than 84 companies in Japan alone making and testing products made by GMOs (FDA 1989) and several hundred in the USA. Most governments are promoting the use of biotechnology as it covers huge markets. Almost all the notable US biologists researching in the area are working in some way with businesses. Genentech's Herbert Boyer tops the list of former University professors turned millionaires, with an estimated fortune of US$ 88 million (Fowler et al. 1988). This could make it very difficult to find really independent expert advice.

Different Universities have decided on various proportions of commercial proceeds to share with inventors. The most generous policy in this regard is that of the University of California which allocates a 50:50 split at all levels of income (Weisbach & Burke 1990). This is certainly a strong incentive for researchers to obtain intellectual property rights, such as patents. The basic research may be channelled to commercial organisations. This technology transfer has been the cause of the establishment of the multitude of companies. The collaboration between University research and biotechnology is at a high level in the USA, and the industrial contribution to academic research is four to five times greater in biotechnology than in other fields. Part of the reason is that there is still much basic biological research required before we understand the details of gene regulation, which is necessary to be able to exploit genetic technology fully.

During 1988 at least 24 US biotechnology companies filed for bankruptcy protection. Within ten tears it is expected that half the 500 US biotechnology companies will be gone. This is occurring long before the companies have refined

their processes or have come up with any products. In fact the delay of several years before there is any product is one of the important causes of bankruptcy. In a survey conducted by Ernst and Young in the Wall Street journal (Gupta 1989) most firms were going to have to reduce their spending levels within the next two years. The key concerns are summarised in Table 10-1.

Table 10-1: Key Concerns of Biotechnology Companies (Gupta 1989)

Concern	**Most Crucial Issue**	%
Finance	Limited R&D funds	19
	Expensive Capital	13
	Other financial	4
Government	Complex regulatory environment	14
	Patents	5
	Reimbursement unclear	2
	Liability insurance	1
Operational	Product pricing	4
	Other marketing	4
	Others have R&D lead	3
	High manufacturing costs	3
	Attract/retain key people	3
	Product lives too short	1
Strategic	Lack of marketing partners	11
	Other strategic	1
Competitive	Competition from estab. industry	8
	International competition	2
Other		2

One of the main reasons is that they have run afoul of public fears, regulation and patents confusion. Few companies expected the negative public reaction. The regulations are also complex. It takes two months to prepare a study for the EPA, which typically takes 5-6 months to review it and approve a field test of a GMO. If any information is left out the process starts again. In a 1990 survey of U.S. researchers and institutes, there were a number who were ready to field test a GMO but because of uncertainty over regulations had not applied to release the GMOs (Ratner 1990).

Another concern that is important is the fear of legal claims. The development of new contraceptives in USA has been greatly inhibited by this, as will be discussed in chapter 11. In the medical field the financial damages have become astronomical. This is also a concern for the use of GMOs. When they are introduced as foodstuffs there should not be any novel compounds in the food, and they are of negligible risk, if approved safe. In the case of vaccines, there is more risk as the vaccine may be of novel structure. Despite the great success of vaccines in combating disease, companies are scared out of research by product liability fears. It has been suggested that we should immunise the manufacturers from these claims so that they will perform such research and introduce useful vaccines (Earley 1990).

Americans are worried that the multitude of small companies could be bought for US$ 6 billion, when the potential is for their sales to be worth much more. There are a number of companies that have been taken over by multinationals, and a few examples are given in Table 10-2. In some of these takeovers the results have been more positive than expected. This is because the increased funds allow freer research into longer term projects involving more basic research, because this is less immediate demand for financial success (Barianga 1990). In addition to the research delays, and regulatory delay, there are long delays for consideration of intellectual property rights. There are about 7,000 biotechnology patent applications awaiting approval in the USA, and it may take 5-6 years to resolve the backlog (Naj 1989).

Table 10-2: Examples of Biotechnology Takeovers (Barinaga 1990).

Company	Founded	Acquired by	Date	Price	Employees
DNAX	1980	SchéringPlough	1982	$29 M	150
Hybritech	1978	Eli Lilly & Co.	1986	$375 M	800
Oncogen	1983	Bristol-Myers	1986	unavail.	209
Genentech	1976	Roche	1990	$2.1 B	1770
GenProbe	1983	Chugai Pharm.	1989	$110 M	166

There is great potential for these methods to enhance the plant breeding industry (Thomas & Hall 1985), and to be a major tool for crop improvement in the future. There are already many types of agriculturally important plants that have been grown with genetic modifications (Gasser & Fraley 1989, Ratner 1989). The range of species is growing, and is limited principally by the ability to regenerate entire plants from genetically transformed cells. The list in mid 1990 included alfalfa, apple, Arabidopsis, asparagus, bananas, cabbage, cantaloupe, carrot, cauliflower, celery, corn, cotton, cucumber, Douglas fir, flax, horseradish, lettuce, lotus, Medicago varia, Morning Glory, Orchard grass, peas, pears, pepinos, petunias, pinetrees, poplar, potato, rape, rice, rye, soybean, squash, sugarbeet, sunflower, tobacco, tomato, trefoil, Vigna aconitifolia, walnut, white clover, with many to join. They will clearly be essential to agriculture in the 1990's and beyond, and that is why major companies such as Monsanto have invested much into producing them. Many seed companies are involved (Ratner 1989).

In 1989 a new commercial product appeared in the United Kingdom, consisting of pairs of frozen beef cattle embryos which are being sold at US$70 a pair (including implantation) to dairy farmers. They are able to implant the embryos into their dairy cattle so that beef calves are produced, which are worth more money, yet maintain the requirement for dairy cows to have a calf each year to maintain the high milk production. The initial annual production will be 50,000 embryos, made by collecting cow ovaries from the abattoirs. From each ovary about twenty useful eggs is obtained, which are subject to IVF. A cow has a 70% chance of becoming pregnant, about the same as the rate for artificial insemination (Newark 1988).

There is a movement in society that wants to refocus attention on less economically-orientated goals (Hallen 1990). If they do become politically powerful, as the Green party in Europe has become, then the situation will change.

There is also a philosophical movement against the rapidity and extent of changes to society, which is opposed to the use of genetic engineering. This reaction is stronger against corporations that are seen to be trying any method to make money without considering other factors. This criticism is justified against some corporations, and will change only if a greater amount of responsibility is felt by them. It may also change due to public reaction which will reduce profits, as is being seen in the consumer reaction against using bovine somatotropin in cows.

People are more suspicious of commercial companies than independent groups. As mentioned before, the OTA survey in the USA of public attitudes to GMOs found that people are more likely to believe environmental groups than companies. This trend may be reflected in the lower public credibility over statements about environmental risks made by commercial scientists compared with government scientists, in the New Zealand public attitude survey (Couchman & Fink-Jensen 1990). People are also probably less supportive of field trials of GMOs if conducted by commercial companies than if they are performed as small scale experiments by University researchers (OTA 1987b).

Agricultural Implications

Increased yields of agricultural products will mean that farmer subsidies for excess production may need to be changed. The average yield increase per year is 1-2%, however biotechnology may allow greater increases. The present production levels have led to a variety of "food mountains", or "milk lakes". Governments have attempted to control this. There will be further exacerbation of these problems so that the area of land required to grow some crops will substantially decrease. This in itself may be environmentally advantageous, but many individual cases will not be. This will change the structure of farming. The first test is the use of BST to increase milk production. It will favour large scale farmers, as discussed later. The way that small farmers can compete is by shifting to higher profit products. For example if BST-milk is labelled as such, which it should be, then small farmers can market their milk to the consumer preference for more "natural" products.

It has been estimated that should BST be used in the USA, by the year 2,000, the U.S. dairy market should require 30% fewer cows, and 51% fewer dairy farms, 195,000 fewer dairy farm employees, and 9 million fewer acres of land for dairy feed production (Banville 1988). In other sectors there may be a shift in farming practise, but it is also inevitable that there is less land, and hence less farmers, required (Kimbrell & Rifkin 1988). Productivity is a ratio of output to input, and it is the increase in productivity rather than production, that is the goal of applying technology in developed countries.

As productivity is increased there will be less land required for agriculture. This may mean fewer farmers. There are already major differences between countries in the size of farms. Anyone who has travelled across the vast farming land of North America must have been impressed with the size of the farms, as will anyone who travels through the countryside of Japan with the tiny fields among the houses. There are obvious reasons for very different production costs, aside from any differences in wages and living standards. There must be questions about whether the new crops, or animals, will be best suited for large scale farming, or

will also be used by small farmers. Society must ask whether it wants to subsidise small farmers and retain their existence, or decide not too, with the social disturbances as the rural community disappears. Where will the limits be placed. There is a limit to this, and productivity is not the only pursuit. When you walk in the big cities of the world and see the social problems, you must ask is it better for people to live in smaller rural communities or not. A few people reject modern urban life and return to communes in the countryside, this is an expression of this idea. We must think in terms of broad social policy about the limits to our development of a modernised world, while also acknowledging the benefits to people that can come from new technology. Perhaps we should develop varieties that can be produced easily by smaller farmers, rather than in the larger farms. This possibility is presented to us by biotechnology, we must open our eyes to alternative ways of pursuing it. We should look at utilitarian ethics, and consider the greater loss of preferences to those who lose their jobs, and vocation, versus the greater number of people who have relatively little to lose from the decision not to switch more to big farming enterprises. We should support the so-called family farms, though we do not need to use the agrarian argument, that farming is a prefered occupation, rather it is protecting people in one particular lifestyle.

This food surplus will have broader ramifications. As food production in developed countries increases, there will be greater surpluses to dispose of. We can hope that benefits are shared by developing countries who, because of their high population growth, will have ever greater shortages of food. The economic system will thus be challenged, affecting much more than agricultural policy.

The initial beneficaries of increased use of technology will be the businesses that receive the royalties for the technology used. In the case of biotechnology they may have invested considerable sums of money in the research, so if we want further research to continue there must be some renumuration of the companies investment. The farmers may be beneficaries of the new techniques if it is cheaper to produce, and less labour intensive. The consumers are also beneficaries as the price of the products falls because of cheaper production costs (Madden & Thompson 1987). A local community where the farming is being conducted also benefits, and conversely a community which does not use higher productivity techniques may suffer. The national economy of a country may also benefit .

Patenting of Life

One concern is over patenting laws. Patents for individual molecules are held by different genetic engineering companies, similar to patents obtained for pharmacological drugs. Of all the biotechnology patents issued in the USA in 1989, about half were for drugs and health care products. The others were primarily for agricultural and environmental cleanup products. The first patent obtained for a living organism was obtained after the court case Diamond v. Chakrabarty in 1980 (Curry 1987). Industrial competitiveness leads to secrecy, and results may not be published until the patentable results are obtained. The closing of results from other workers is against the principle of scientific openness. On the positive side, the financial interest has created more funding for research (Yoxen 1987), and faster overall progress in research in these areas has been the result of the intense research

efforts.

Patents can generally be sought either on products or processes used to manufacture the product. It is easier to obtain a process patent, but it has been harder to prove that a competitor is using your process, as access to their production facilities may be restricted. The US Process Patent Law, effective from February 1989, shifted the burden of proof in process patent cases from the company with the patents, to the importer of the competing product. The importer must prove that they are using a different process. There are still differences between the systems used in Europe, USA and Japan, as well as other countries (Cook 1989). For example, under the old US patent system inventors can apply for US patents any time up to a year after the disclosure of their finding (e.g. in a scientific journal), but in Europe or Japan, prior publication invalidates the claim. It is likely that this grace period will be removed, so that many more research results will be first published as patent applications, before they appear in scientific journals (Hodgson 1989b).

During 1987 the US Patent and Trademark Office made the following announcement: "The Patent and Trademark Office now considers non-naturally occuring non-human multicellular living organisms, including animals, to be patentable subject matter ...". The conflict between economic advantage and moral objection is further highlighted in the granting of animal patents. Some animals are now under patent, the first patent to be issued for animals, applies to all non-human animals made containing an activated oncogene inserted by genetic engineering techniques, and was based upon one such mouse made, later called "Oncomouse" (Editorial 1988) It was U.S. Patent number 4,736,866 (Clark 1989). These animals can be used as more suitable research "materials" for testing sensitivity to carcinogens. Du Pont, the licensee of the Harvard patent, is taking orders and selling the mice at US$50 an animal. The question of the patenting of animals is very contentious, and there have been some major studies on it (OTA 1989). After the Oncomouse patent, 29 congressmen sent a letter to the US Patent Office labelling the decision as "arbitrary and capricious". Both the Senate and the House of Representatives have considered bills calling for a moratorium on patenting animals. Over forty other applications were held up while policy decisions were made.

The legal situation varies between countries, but it appears that there will be an increasing number of animals under patent in the United States. The OTA Report said that existing regulations can be adapted for most of the practical considerations of animal patenting, such as whether farmers should pay royalty fees for breeding patented livestock. There had been earlier attempts to obtain animal patents, but they were hampered by the lack of a precise definition of how to repeat the procedure. The claim of the "Oncomouse" patent is worded: "A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at the embryonic stage." It is precisely worded, and based on a genetic description, which is the reason it was accepted (Clark 1989). The first step in the creation of such an animal is easily definable, so that a chance mutation on a farm is not going to violate the patent. The deposited item is actually the plasmid used in transformation, which is sufficient, rather than embryonic cells. Classically bred animals might be protected by animal variety rights legislation, but it is unlikely that they could be patented.

There have been several pieces of legislation proposed in the USA to regulate

animal patents, ranging from a ban on them, to a system with similarities to plant variety act legislation (Czarnetzky 1988). Under the Animal Patent Act, a patentable animal is an organism with one or more characteristics that are distinct from all other known animals. The US House of Representatives passed a bill in 1989 which, if enacted, bars the granting of patents to humans and provides for a farmer's exemption from patent infringement with respect to transgenic farm animals. The only standard exception to the US Patent Office's "anything goes" interpretation of the law on the patentibility of animals lies in the reluctance of the US Patent Office to allow a claim to an animal broad enough to encompass human beings. The Commissioner has asserted that the "grant of a limited, but exclusive property right in a human being is prohibited by the Constitution" (Armitage 1989). A legal point that has not been defined is what is the definition of a human being, in the case that animal-human hybrids are made (Fishman 1989).

There are two basic approaches to applying patent law to biotechnology inventions. In the USA the normal patentibility criteria shall apply, that is the invention has the attributes of novelty, non-obviousness, and utility, and the invention should be deposited in a recognised depository. The second type of regulation is to apply special criteria. While a country may accept the first type of criteria, some countries have specifically excluded certain types of invention. This is the case in the Europe Patent convention, and in particular countries such as Denmark which have stronger worded exclusions.

According to European Patent Convention Article 53(b), microorganisms are patentable, but "plant or animal varieties or essentially biological processes for the production of plants and animals" are expressly barred. Since the animals need to be reproduced by a natural biological process, reproduction, then they can be regarded as unpatentable. However, property rights have long been recognised for breeding animals such as prize bulls and racehorses. There are still signs in 1989 that moves are underway to make animals potentially patentable in Europe, even though the European patent office in Munich has turned down the application for a European patent for Oncomouse. It is possible to interpret the clause 53(b) in a different way, and the OECD has recommended that this be done. In this case a new plant or animal would be considered a new variety only if it was explicitly described as such (Dickson 1989a). There is public rejection of the idea in some countries, and there is an explicit law in Denmark against animal or plant patents. The European Council has drafted a directive to change the laws on biotechnology patents. The draft declares living matter is no reason for nonpatentibility. Animal or plant varieties will not be patentable, but the insertion of a particular segment of DNA into the genome of a seed will still be patentable even if the resulting new plant constitutes a variety and is not itself patentable (Whaite & Jones 1989). At least ten countries permit animal patents, including Japan and Canada, and another 53 have not prohibited the granting of patents (Lesser 1989).

It is important that patenting protection does not prevent the widespread application of important new strains. This includes both those organisms important for scientific research, and the increasing number of new agricultural varieties that have been made. Many companies are involved in the work solely for the fortune that they will make from using what are essentially natural genetic resources, which are merely moved around. There has to be some limit to how the patents are enforced, especially in areas such as agriculture where companies could be seen to

be making a profit from world food needs. However, these are conditions that could be practically solved, and similar problems have been dealt with plant variety licensing in many different countries. A recent OECD report highlights the finer details of competition policy, and the law will need further development in the area of biotechnology patents. Monopolies on patents are discouraged, but there will be complications with patents and agreements with farmers (Phillips 1989).

Public Attitudes to Patenting

There is an unresolved ethical question whether corporations have the right to create and patent new forms of higher life for profit. Just because courts in some countries support the patenting, it does not resolve the ethical dilemmas. In the USA, the constitution, a document 200 years old, is applied to this question and used to justify the patenting of lifeforms. This does not necessarily provide any ethical answer to the question. It may be consistent with existing capitalistic ideas, and support inventors to encourage creativity, but this does not solve the underlying question. The question is whether the limit of applying patents has been reached with the case of animals, or will the limit be placed at humans? The opponents of animal patents include animal rights groups, and people who have a high inherent respect for animals such as religious groups.

The public attitudes to the patenting of different types of things, including living organisms was measured in New Zealand. The results are presented in Table 10-3. 90% of the public had heard of inventors being able to obtain a financial reward through patents or copyright. Those who had heard of patents or copyrights were asked if they agreed whether patents should be obtainable for the five classes of items (Couchman & Fink-Jensen 1990).

Table 10-3: New Zealand Public survey (Couchman & Fink-Jensen 1990). The survey of the general public was conducted with face-to-face interviews, the rest were written questionnaires among different occupation groups. Of those people who had heard of patents, the question was asked, how many agreed that patents should be obtainable for the following areas:

Obtain patents for:	Occupation of Respondents, and % in agreement:			
	Public	Teachers	Farmers	Scientists
New inventions	92.5	88.1	93.9	95.3
Information	84.6	71.8	82.2	80.6
New plant varieties	70.8	49.1	82.7	65.9
New animal breeds	59.1	50.9	68.5	62.8
Genetic material	51.2	33.9	64.5	53.1

Many people think that the patenting of new information is acceptable, but there was less acceptance of patenting of new plant or animal varieties, and very low acceptance of the phrase "genetic material extracted from plants and animals". There was more acceptance of patenting of genetic material among those who thought there were benefits to New Zealand of genetic engineering. There was less acceptance of patenting among the age group 15-24 years old. The perception of unacceptibility can translate into protest action, and campaigning groups, which create greater

pressure than there numbers. The negative reaction does continue to reflect the general feeling that genetic material is special, and should be different to other types of information. The negative reaction to the patenting of living organisms and genetic material extracted from them was shared by scientists and science teachers, but not by farmers. The fact that farmers were more supportive of such patents suggests that they do not see patenting or variety rights as a problem to prevent them using protected varieties. This may somewhat negate the claims that patenting is bad for farmers, as they know that they can use new varieties of crops or animals on their farms, and they are interested in the development of better varieties from an economic view, it is their living. Because New Zealand law does not contain any list of excluded subjects, such as plants or animals, they are in principle probably patentable.

The Ethics of Patenting Animals

We should examine the ethical arguments that are commonly expressed when talking about patenting of animals. The ideas have been discussed throughout this section, it is useful to list the key points.

The major arguments for patenting animals include (OTA 1989);

* Patent law regulates inventiveness, not commercial uses of inventions
* Patenting promises useful consequences (e.g. new products/research)
* Other countries support patents, so our country needs to if the biotechnology industry is to compete
* If patenting is not permitted, useful information will become trade secrets
* Patenting rewards innovation

The arguments against animal patenting include;

* Metaphysical concerns about promoting a materialistic conception of life
* Patenting will lead to increased animal suffering
* Patenting promotes inappropriate human control over animal life
* Some countries do not permit animal patents
* Patenting promotes environmentally unsound policies
* Patenting produces excessive burdens on agriculture (increased costs to consumers, payment of royalties for succeeding generations)

Most of these issues will not be affected by permitting patents, as the issues are similar to those existing prior to the patenting debate (e.g. animal rights, adverse effects of high technology on agriculture, the distribution of wealth, international competitiveness). This issue remains contentious and the fact that different countries have conflicting policy reflects this. The issue is closely related to the commercialisation of genetic engineering, but some sort of breeding protection is already accepted for farming, we need to ensure that farmers can continue to use new animal varieties and that the research that produces them is paid for so that there is an incentive to develop new varieties of benefit to society.

Patenting of Genetic Material

As stated to qualify for a patent an invention must be novel, non-obvious and useful. If the claimed invention is the next, most logical step which is clear to workers in that field, than it cannot be inventive in the patent sense. If a protein sequence is known, than the DNA sequences that code for it will not in general be

patentable, unless there is a sequence which is particularly advantageous, and there is no obvious reason to have selected this sequence from the other sequences that code for the protein (Carey & Crawley 1990). The invention must also be industrially useful. In the case of natural products there are often difficulties because many groups may have published progressive details of a molecule or sequence, so it may have lost its novelty and nonobviousness.

There are some patents on compounds that have a relationship to genetic material, such as chemicals 5-fluorouracil which is related to ordinary nucleotides. It is an antiviral agent, and integrates in DNA, but is essentially the same as an ordinary drug. There are patents on short oligonucleotide probes used in genetic screening. These are essentially short pieces of the human genome. There are also patents on protein molecules which have medical uses, such as erythropoietin. In this case the protein structure is patentable if it, or the useful activity, was novel when the patent was applied for. If someone can demonstrate a use for a larger piece of DNA than they can theoretically obtain a patent on it. An example of a larger patentable section of genetic material would be a series of genetic markers spread at convenient locations along a chromosome (Saltus 1986). If the molecules are new, non-obvious, and can be chemically defined and their use described, then they are individually or collectively patentable. Another set of genetic markers can be found on the same chromosome and separately patented if they also meet those criteria.

There are different areas for which a patent may be obtainable. The direct use of products, such as therapeutic proteins, is well established. The information may be used in the study of a particular disease. An example of this is the introduction of a gene into an animal to make the animal a model of a particular human disease, and it was for this reason "Oncomouse" was patented. A third field is the use of genetic information to cure a disease, for example using the technique of gene therapy with a specific gene vector. However, with the completion of the genome sequence of many organisms, including humans, any new genetic material will no longer be novel as it will be available in a database (Carey & Crawley 1990). If researchers decided to apply for patents on every new protein sequence, they may also fail because of the lack of fulfilling the usefulness criteria. It is therefore likely that in the near future patents will be difficult to obtain on gene products, though it is expected that prior to the sequence determination there will be many applications for these different types of patent.

There are major questions which remain unclear, such as the scope of patents. Whether altering a few amino acids in a protein to improve the efficiency is patentable and the limits of this. Such changes may be obvious to anyone with knowledge of enzymology and may fail under that aspect of patent requirement. The issues of infringement of existing patents is also difficult, as new methods to effect similar genetic changes are developed (Adler 1989). The interaction between the system of plant variety rights, and the newly emerging area of animal variety rights, is important. Patent laws are very important as they influence the pace of developments in biotechnology, and are a fundamental part of the driving force behind the new technology. However, such decisions are also political,and will remain so (Smith 1988).

Third World Interests

Biotechnology is a global issue. It can be used in positive or negative ways. It is most likely that it will be similar to other technologies and serve the interests of the rich and powerful more than it serves the needs of the poor. As it becomes commercially tied to companies which enforce patents or protection rights it is not likely to aid the third world so much as it would if equal access was given and may be inconsistent with human welfare. There is much potential, such as for universal vaccination programs and improved crops, but the companies will be trying to make a profit - that is their function. The solution probably involves the use of United Nations agencies that could provide a fairer distribution of benefits. New crops do have associated problems, they may aggravate genetic erosion, and accentuate inequalities in the farming population. Farmers will become more dependent on transnational agrobusinesses (Bogeve 1987, Fowler et al. 1988).

The potential impacts of advances in biotechnology will not only be irreversible, but they will introduce major and unpredictable changes in the global organisation and distribution of production. Countries which rely on the export of high value commodities are likely to be affected by these advances. Since the growth of agricultural complexity in the sixteenth and seventeenth centuries there have been plant and seed collectors who have taken useful plants to Europe and North America. In fact, plants were collected and planted for their products by Queen Hatsheput of Egypt in 1495 BC, and there are worldwide examples of such movements. The appearance of botanic gardens in Europe in the sixteenth century aided this process. An interesting example is that from a single coffee tree in the Amsterdam gardens came the seeds to plant most of the coffee in South America (Juma 1989). The movement of plants is closely associated with major European empires as a basis for more economic expansion. Thomas Jefferson said "the greatest service which can be rendered to any country is to add a useful plant to its culture". This idea is still being pursued, which has and will continue to have, a powerful effect on third world countries. The raw resources of the new biotechnology industry are genes, which are often introduced from third world countries with no renumeration. The gene banks and germ plasm stores are mostly under the control of developed countries.

There are a few examples of technology transfer to the third world. One interesting example which was cited by Gibbons (1990) is the use of potato tissue culture in a remote Vietnamese village, in people's homes. Important routes of technology transfer include the sending of students and scientists from the third world to do research in laboratories in the developed world. One cited reason for a failure to transfer to the third world from biotechnology companies is that many third world countries are under no obligation to follow the patents issued elsewhere, so companies results can get stolen if they were to transfer them there, hence they do not. There will always be a conflict between financial interests and human welfare, one of them has to be compromised. A danger with the long regulatory delays in developed countries, is the people in the third world may directly try GMOs if they are seen to be needed.

The medical advances using new genetic techniques do have implications for the hird world. More than other types of medical research in new technology,

genetic engineering should contribute to health. While genetic screening services are in the distance in developing countries, they will come, when cheap screening methods have been developed. For example the use of the polymerase chain reaction (PCR) to amplify DNA means that radioactive DNA probes do not need to be used (radioactive isotopes may not be available, as well they decay), rather colourimetric enzyme assays can be linked to the tests. This offers much promise. The research in tropical diseases will be aided. The development of safe vaccines will also be of great benefit.

The genetic information, especially of the human being, belongs to all humanity. The benefits that come from its discovery and use should show us how all humanity is one. We will see how the genetic constitution of all humans from different races is the same. We will see how all of us have mutations, no one is perfect in their genetic structure, or should I say perfectly normal. Decisions on the use of genetic manipulation in one country will affect other countries, because people move, change their countries. It is therefore imperative that the decisions about any future germline genetic manipulation, especially of humans, take into account people's opinions worldwide. This may be best handled by an international forum, which national committees should interact with.

11. Human Reproduction

Birth Control Policies

During the past decade media attention regarding human reproduction has focused on *in vitro* fertilisation (IVF), a technique which has resulted in the birth of around 20,000 children to infertile couples. The amount of media attention given to infertility aids is much greater than that given to the more important question of trying to control the excessive fertility of the human race. In the last decade this has affected several billion individuals. That does not mean that the problem is literally a hundred thousand times more important, but it does highlight the importance of birth control.

We have a situation in the world today that it is rapidly approaching overpopulation. The population rises at a rate of over 400,000 per day (Aitken & Lincoln 1986). There are thought to be 600 million couples of reproductive age in the developing countries, 80% of whom, do not use adequate means of birth control (W.H.O. 1984). The situation is such that if we do not decrease the birth rate now, we will have very serious overpopulation problems. Fortunately during the last two decades many steps have been taken which have slowed the rate down from what it was, but there is still much more effort required in many countries. Many other interrelated problems may confound the primary problem of overpopulation, such as pollution, lack of food, human selfishness, and the loss of densely populated and agriculturally important coastal land with urban sprawl and as the sea level rises.

In earlier times the infant mortality rate was very high, but now in most countries it is much lower. This means to replace the population not more than 2-3 children per couple are required, much lower than the possible reproductive potential of the average human couple. In order to manage the population, contraception is required. Most couples are concerned with contraception. An additional factor is that the increase in extramarital sex has meant that contraception is particularly important for all young people, in both industrial and developing countries, whether or not we agree with extramarital sex. There are many very harmful social problems as a result of high incidence of extramarital sex, but contraception is still desirable to avoid passing these problems to a new individual.

Methods of Birth Control

About 500 million people used contraception in 1988. The policy chosen depends on the country as to the method and acceptance. In China a one child per couple policy is strongly encouraged. In Shanghai, couples may have to wait several years for a ticket for permission to have a child. If a second child is born, the penalty is three years average earnings, which is a policy which discriminates against those who are poor. Detailed studies of the one child policy actually suggest

a better policy now may be to allow two-children with a gap between their births, as this will give a better population age structure in the future (Greenhalgh & Bongaarts 1987). The best policy however will depend on the time and country, what is essential is that birth control is used, and especially in the poorer developing countries. It is irresponsible stewardship not to use it.

Sterilisation is one method of contraception, being used by 130 million couples in the world in 1983, making it the most widespread form. The main type used is female sterilisation, even though it is more risky, and more expensive than female sterilisation. Vasectomy is used widely only in USA, United Kingdom, India and China. There are some countries with rapid birth rates that do not use sterilisation, such as Latin America and most of Africa. This is because of the objections to its use by the Roman Catholic church, and some politicians.

Unlike the development of most other products, which is regulated by the actions of the marketplace, the development of new contraceptives is influenced by other conflicting public policies. The combination of public policies and the complexity of evaluating their risks and benefits, has lead to slow development of new methods. Developed nations offer much more support for research to alleviate specific illnesses than for birth control (NRC 1990).

There have been very few developments in the methodology of contraception during the last two decades. In the USA there have been no new active ingredients in the birth control pill sold since the 1960's because of fears of legal costs if there is any adverse effect. The birth control pill, in old or new form, is not widely available in Japan because of the opinions of the Medical Association. In Europe three new ingredients have been introduced in the 1980's, which can be used at much lower dosage levels, and are in fact safer than old formulations. There is currently very little research into contraceptives which is due to a lack of commercial interest by pharmaceutical companies (Djerassi 1989). Companies do not do research if the potential risks of liability and the costs of protecting against it are not balanced by a sufficient profit potential. The only way to change this is to change the system of liability payments that companies are vulnerable to. There is a need for more research, and new possibilities could include a new spermicide with antiviral properties (to avoid AIDS), a once-a-month pill as a menstrual inducer, and reliable ovulation predictors. More distant may be easily reversible and reliable male sterilisation, a male contraceptive pill and an antifertility vaccine.

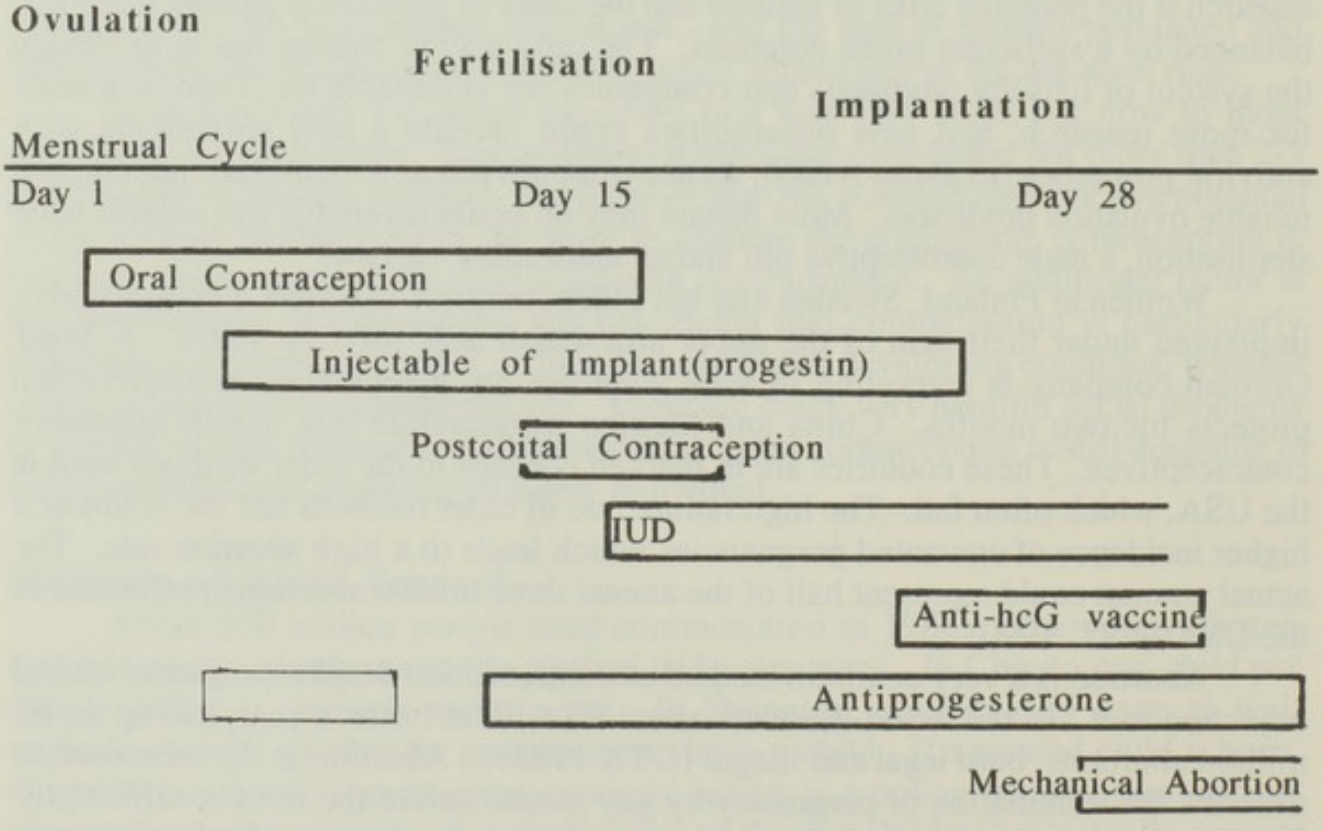
Women in Finland, Sweden and ten other countries can have a contraceptive implanted under their skin of the upper arm which acts for five years. A West German company is marketing in forty countries an injectable contraceptive that protects for two months. China and Mexico manufacture one month injectable contraceptives. These countries are in marked contrast to the older methods used in the USA, which often fail. The high failure rate of older methods has the result of a higher incidence of unwanted pregnancies which leads to a high abortion rate. The actual amount could represent half of the annual three million abortions performed in the USA (NRC 1990).

Abortion is a very common method of contraception despite the greater ethical objection to it. In the world there are about 90 million births a year, and up to 60 million abortions, both legal and illegal (OTA 1988c). Abortion is the term used to describe the termination of pregnancy by any means before the fetus is sufficiently developed to survive (6 months by the best medical techniques). Abortion is a very

sensitive ethical and political issue. It does need to be considered for extreme circumstances, with the view that we may have to make compromises in a world like ours, as discussed in the last chapter.

Abortion is the least preferable of birth control methods. Between contraception and abortion there is the technique of what has been called embryo arrest. The time periods that different methods of fertility control act on is summarised in figure 11-1. Contraception is definable as the prevention of conception. Some birth control methods currently called contraceptives can only act after fertilisation. Post-fertilisation interruption is a very common process that most women have experienced at some time, even though they may not be aware of it. Contragestion, is an abbreviation of contra-conception, and has been suggested as an appropriate term to use for describing the action of some agents, such as RU-486 (Baulieu 1989). Some make implantation impossible, such as Ovran and Eugynon-50. The IUD has been also thought to prevent implantation. It is a serious legal and ethical issue to decide whether agents acting several weeks after conception, such as RU-486, are abortive drugs or ones that cause embryo arrest. Probably not until the embryo is implanted, after 14 days, should we call the action abortion (Crystal-Kirk 1989), though it is still seen by some as unethical. The abortion laws in New Zealand, Libya, and West Germany, apply specifically only after implantation, 14 days, which is consistent with this thinking.

Figure 11-1: Methods of Fertility and Birth Control The efficacy of the different treatments is represented at the time after ovulation shown in the figure. The thick lines indicate the time of maximal effect, and the light lines indicate whether accessory effects may occur (Adapted from Baulieu 1989).



Recently, the steroidal antiprogestin milepristone (RU-486) has been developed and this has been used widely as a menstrual inducer in France. It has a high affinity for the progesterone receptor. Prosgesterone is a hormone that isproduced in pregnant women and is necessary for the maintenance of pregnancy. The hormone binds to a receptor on the target cells, and it is this binding which is necessary to act as a signal. RU-486 prevents this binding, thus removing the influence of progesterone, allowing menstruation to occur, which will take with it the early embryo (Baulieu 1987). It will aid the induction of menstrual flow 6-8 weeks after the last menses; like a spontaneous abortion in action. The treatmentconsists of three 200 milligram pills of RU-486, followed 48 hours later by a small amount of prostaglandin to induce menstrual flow. The procedure is successful in 99% of the cases, and its efficiency is being improved. However, it must be performed under medical supervision in accordance to the developed procedure, and is safe only in countries with well developed medicine.

This technique is very useful in countries where surgical experience is limited, as most women will be able to avoid any instrumental intervention, with concurrent reduction in the risk of infection or injury. However, due to intense pressure from anti-abortion lobbies the company has been slow to use it outside of France, and it was even removed from the French market until the government forced its introduction. It was developed at the end of the 1970's, but was only used for the public at the end of 1988. It was used by over 25,000 women in the first year of its use in France, in preference to surgery (Palca 1989). It is currently being used on over 1,000 women a week. A trial in the U.K. has found it safe (Guillebaud 1990), and it is likely that it will be used in 1991 in the U.K., as the company Roussel-Uclaf has applied for a license. The U.K. government will probably support the application, because not only is it medically efficient and safer, but also more convenient for the women, and cheaper for the government (it could save £10-15 million annually). After the U.K., Scandinavia would probably be the next country. The company will introduce the drug to countries were abortion is not very controversial.

Perhaps the W.H.O. can introduce it more widely, as it could save many dangerous illegal abortions which cause the annual deaths of about 200,000 women worldwide. In some countries almost 50% of the maternal mortality is due to unsafe abortion. W.H.O. is also researching another drug, ZK98734, but it may not be as efficient. China has approved the use of RU-486, but since the French will not supply it, the drug may need to be synthesised in the countries that decide to use it. One of the limitations of the use of RU-486 is that it must be used with synthetic prostaglandin, made using genetic engineering. The unavailability of synthetic prostaglandin may keep the drug out of Canada and Australasia also. China is the only developing country with access to prostaglandin. The American Medical Association supports the trials and use of RU-486 in USA, despite the opposition from the pro-life movement.

There has been research aimed at developing vaccines to control fertility (Ada et al. 1985, Aitken & Paterson 1989), and this is one of the most urgent needs for medical research. The ideal vaccine should have a long lasting specific effect and should inhibit fertilisation as a contraceptive agent, rather than act as an embryo-arresting agent, or an abortificant. The immunological response induced by the vaccine should not elicit any cytotoxic response that might result in abnormal

reproduction or damage. Long term contraception in female mice has been achieved by vaccination with antibodies to the sperm-binding proteins of the zona pellucidia, the membrane that surrounds growing oocytes and ovulated eggs. One of the proteins that sperm bind to has been sequenced, and a 16 amino acid sequence of this protein was synthesised as a peptide. This peptide was coupled to a carrier protein and injected into female mice. The mice made antibodies to this peptide, which were found to be an effective contraceptive. Repeated immunisation with this peptide resulted in long term infertility (Millar et al. 1989). The sequence of the equivalent human peptide is known, and is being tested. There are similar experiments underway in human embryo research.

Should We Use Contraception?

There has been a long history of contraception, there are prescriptions for contraceptive pastes in Egyptian medical papyri from 1850 B.C. Soranus of Ephesus (78-117 A.D.) wrote a detailed account of contraceptive methods, which he distinguished from abortive potions (Soranus I). The male sheath, or condom, was made in a linen version by Gabriel Fallopius (1523-1562), the discover of the fallopian tubes. Public interest in population control was widened by the essay in 1798 of Rev. T.R. Malthus, *Essay on the Principle of Population as it affects the future Improvement of Society*.. The first birth control clinic was opened in Amsterdam in 1882, and in America in 1916 (Wilkinson 1988).

Many recent books on ethics do not consider contraception, except the Catholic theologians, as it already widely accepted. However, it was only widely accepted during the second half of the century. Contraception for medical reasons has long been permitted by many Christians, and by some Jews. It is not accepted by Jewish Rabbis generally, and recently they have been opposed to it as they are trying to build up the Jewish population (Jakobovits 1975). Jews consider the Biblical precept to "be fruitful and multiply" to mean that each couple should have at least one son and one daughter as a minimum duty.

This is an area where there is a major controversy in the Roman Catholic Church, whereas Protestant Churches in general support birth control through the use of contraceptives. The Catholic church and other religious groups who exert powerful control over the actions of many people, carry a huge responsibility for the failures to decrease the global population problem. We need to examine this case to decide which principle should be given priority when several apparently clash. There are several important ethical principles involved, stewardship of the earth and a high value of human life are common to a general perspective and a religious perspective. For those who hold religious beliefs, the commandments of God to mankind, recorded in the Bible for a Christian, are also important, and can be overriding to some believers. In the Bible, humans were told to be fruitful and multiply and reproduce (Gen. 1:28). All people would agree that the procreation of the new generation is necessary to replace the old, and is the basis of family structure and society. The old, who are wiser, train the young who replace them. However, the human race was also repeatedly told to take care of the world, and to be good stewards (Gen. 2:19).

The *Humanae Vitae* of 1968 (Pope Paul VI) has been used to maintain the Catholic teaching that every contraceptive act is intrinsically evil. It is based on the idea that intercourse is a single act with two aspects, the unitive and the procreative,

which it claims are inseparable. Some Catholic theologians have since considered that contraception is intrinsically evil and others have considered that it is possible to dissent from the papal teaching on contraception (McCormack 1981). The major argument used by opponents of this view of the function of marriage and intercourse, is that the primary function of marriage is the unity of man and woman (Berry 1987). Only out of this primary function of marriage is that of procreation, Eve is not viewed as a baby-maker for Adam, but as an equal companion. No where in the Bible is contraception prohibited, despite the existence of the methods. However, it has been opposed since the time of St. Augustine.

Sterilisation is permitted by Catholics only if it is part of a procedure necessary for the treatment of a serious disease such as cancer. It is regarded more seriously than individual acts of contraception. The Roman Catholic church says only the periodic abstinence method can be used. However, even this abstinance can be argued as unnatural. All medical treatment is unnatural, but that does not make it wrong. We are not merely to follow the law of biological laws and rhythms as is suggested by the narrow interpretation of Catholic "natural law", it is in conflict with the responsibility of stewardship.

Some racial groups, or countries are very sensitive to the encouragement of birth control by what they see as the major world powers, however, fortunately most people do see that it is a real problem for everyone. It has worked in some countries such as Indonesia, but failed in others like Kenya. Some object because it may encourage promiscuity,an argument used by religious authorities, and some governments such as Japan, but abuse of a practice does not cancel its proper use.

There is another reason to allow birth control, as mentioned. This is the very high incidence of maternal mortality, connected with pregnancy, abortion, and child birth. In Africa, a woman has a 1-in-14 lifetime risk of maternal mortality (in developed countries the figure is between 1 in 4,000 to 10,000). The WHO is trying to tackle this problem, which on a per capita basis works out to cost about US$ 200 per maternal death saved. There needs to be more access to family planning clinics in developing countries. Some governments are against this, some for religious reasons. If they look at saving lives from illegal abortions, which are often the result of unavailable birth control, they may change their thinking. It also represents the usual problem of misdistribution of wealth.

We need to take responsibility for our actions, including reproduction. There is extreme over population in parts of the world, and even if we all slowed down today, the carry on effects will take another 50 years to stabilise, due to the great proportion of young people in the worlds age structure. It is an additive cause for much starvation and suffering, and a major cause for some of the pollution problems. When the earth is crowded, and so many resources used, we should not overfill it. There is a limit to the land. We need to control the desire to have many children, and what is more important allow choice to those who want birth control, and use reason and common sense, and the techniques that we have been given in our technology to practise sensible birth control.

Infertility

Is Infertility a Medically Treatable Disease?

There are many couples who are unable to have children. The proportion is approximately 10% (H.M.G. 1986, OTA 1988c). For the purposes of this discussion I will use the convention of calling them infertile. Physicians have developed methods to overcome infertility, with the motive of helping such couples have their own child. In some countries the assisted reproductive technologies such as IVF and AID are involved in close to 1% of the live births. The birth of children to infertile couples brings not only great human joy but a new human being. We should also recognise the frustration of couples who desire to have a family genetically related but are unable to achieve this on their own. In our society there are many prenatalistic ideas putting pressure on couples to have children, and there is a shortage of children for adoption (though this has not been aided by the racial selections in the procedure endorsed by some hospital boards). These medical treatments are the means of raising children for many couples who were not able to give birth to children. All methods for the procreation of children should always have the well being of the family in mind, though we should also enjoy the joys of parenthood.

We can't reject these techniques as "unnatural" because we would then be rejecting modern medicine as a whole, as every medical treatment is aimed to resist disease and suffering. Some critics such as Paul Ramsey or Leon Kass, argue that infertility is not a disease in a strict medical sense, and the physician who employs IVF to overcome infertility is merely treating the desire of the couple to bear a child. It is manufacture, not medicine in their view, however, it depends on our criteria of health, in the wider sense it is restoring a natural function of the human body. They are seen by many as another application of intelligence to overcome our adverse situation.

There has been a concern about the capacity of technology to change, not just the conditions of human existence, but its essential characteristics (O'Donovan 1984). What has occured with reproductive technologies is a revolution in our view of human reproduction (Jones 1987). The writings of twenty years ago were mainly against IVF, but now most writers see it as ethical for use by married couples. It is not a matter of being conformed to the world, but rather the value of hindsight and understanding upon a technology. There will always be techniques and ways to make us inhuman, what could show this more than war, rather we must look at the techniques with eyes of the 1990's.

In the United Nations Declaration of Human Rights, one of the "rights" is to raise a family. However , this refers not to infertility but is against compulsory sterilisation. A negative right not to be interfered with (e.g. the right to marry), does not entail a positive right (e.g. society must provide a spouse). An individuals' right to reproduce is not violated if fertility treatments are not made available. This question is important regarding the limits of public funds for some reproductive methods. Currently many countries offer support for married couples to use these techniques, but those involving ova or sperm or embryo donation are not financially supported in France or the USA. When health care budgets are stretched, the

money will be spent on what are generally seen to be more urgent needs.

There are various factors that contribute to infertility. Among women the three most common are problems in ovulation, blocked or scarred fallopian tubes, and endometriosis (the presence in the lower abdomen of tissue from the uterine lining). Among men most cases of infertility are due to abnormal or too few sperm. The causes include genetic factors, environmental pollution, drugs and smoking, and much is yet to be known. About twenty percent of cases of infertility in the USA are the result of infection with sexually transmitted diseases, which are often the result of sex outside of marriage. There are various ways to overcome infertility, including induction of ovulation, surgery, and AIH or AID, which may be used in 85% of cases. The use of IVF and GIFT may treat 10-15% of cases. Approximately only half of infertile couples can achieve a pregnancy, sometimes this is because they run out of money trying these techniques. They have to realise there is a point to stop. In 1987 in USA about US$1 billion was spent on medical care to cure infertility, about 7% was on IVF (OTA 1988c).

Methods Involving the Married Couple Only

There are several methods used to alleviate infertility. The oldest involving only the married couple as sources of gametes is artificial insemination (AIH), where semen of the husband is implanted into the wife. The oldest recorded case was in 1790. There was some ethical debate, but it is generally accepted as a legitimate medical technique by the majority of people including the majority of Christians (Dunstan 1975). The exception is the Roman Catholic church (Vatican 1987), rejecting any technology that would replace sexual intercourse between husband and wife, including artificial insemination and IVF. They reject them for the same reason as for contraception, that they separate the procreative and unitive aspects of intercourse. However, Catholic hospitals in several countries will continue to provide these services, as they do not accept that aspect of the Vatican policy.

The technique of IVF is of much more recent origin. Human IVF is an established clinical procedure in many countries. Attitudes have changed as it has been found that the babies born by use of IVF are normal and it has brought happiness to many families, so that now it is also generally accepted as a legitimate medical treatment. Because of much publicity this technique is well known, and over 20,000 babies have been born as a result of it.

There are several major phases in the technique of IVF (Edwards 1985). First the woman is treated with a stimulator of follicular growth, then the oocytes, or egg cells, are removed by aspiration and collected. The oocytes used to be collected by a technique called lapraroscopy, where the oocytes were aspirated from the follicles in the ovary. There has been increasing use of ultrasound scanning to guide the needle which can then go through the abdominal wall or the vagina, therefore avoiding the need for repeated operations (Sims 1988). Male semen is combined with the oocytes to fertilise the eggs, there is a high success rate, often 80%, for patients to fertilise the eggs. Usually about 10-12 embryos are produced, and these are grown to a multicell stage before implantation. Implantation is the most difficult stage. The two most important factors are maternal age and the number of embryos replanted. In the successful clinics, 3 embryos are normally replanted with the rest of the embryos being frozen, to be used for another attempt to produce a child (the first

babies born from a frozen embryo are growing normally).

With the replacement of 3 embryos a 33% implantation rate is often obtained (Trounson & Wood 1984, Edwards 1985). The United Kingdom the Voluntary, or Interim, and now-called Statutory Licensing Authority, records the statistic from the IVF clinics. It reported that the overall pregnancy and live birth rates for 1986 for all IVF clinics in Britain were 9.9% for pregnancy and 8.6% for live birth, per stimulation cycle, and in 1987 this figure was 9% for live births. The figure per embryo transfer cycle is 12% live births, in 1987 (VLA 1989). Usually women have several cycles of treatment so the success rate is about 25% overall. There is a wide difference in the success rate between different clinics, depending on experience, and the selection criteria for mothers. There is still much room for improvement in the success rates of the technique, which requires further experimental research.

A recent alternative is gamete intrafallopian transfer (GIFT), in which the mother receives hormonal treatment to stimulate ovulation, and produce several ova. Some of these are then placed, together with a concentrated amount of a sperm, in her fallopian tubes. Fertilisation occurs normally, in the body. If it can be made to be safer than IVF for the mother then it should be used. GIFT is not applicable to all women requiring IVF, as at least one functioning fallopian tube is required, so it will not replace IVF totally. A new technique is called POST (peritoneal oocyte and sperm transfer). A mixture of eggs and sperm are placed at the end of the fallopian tube in the peritoneal cavity. VISPER (vaginal intra-peritoneal sperm transfer) is where the sperm is placed directly in the peritoneal cavity. They are simpler than IVF in the fertilisation and embryo transfer side, but the same hormonal manipulation of the women is needed. In practise the techniques are done in parallel in the same units (Sims 1988). GIFT has a higher success rate, of 19% live births per cycle, versus 10% live births per implantation using IVF, in 1987 in the United Kingdom. The multiple pregnancy rate is about 20% in both. The actual success rate of IVF is about the same as it was in 1985, though new clinics improve as they gain experience. The figures for the UK in 1988 showed that clinics varied considerably, with the highest live birth rate being 16.4%, with a mean success rate of 12.9%. However, some smaller clinics had no success at all, and the Interim Licensing Authority, soon to be replaced by a Statutory Licensing Authority, has threatened that it may withdraw the licenses of those clinics (ILA 1990).

In the United Kingdom there is a total of 42 IVF clinics, 38 offer GIFT, and about 32 clinics offer GIFT alone (VLA 1989, ILA 1990). There is a growing number of clinics offering GIFT alone, in March 1990 there were 45 unlicensed clinics only offering GIFT. Whichever technique is in the best clinical interests of the mother is used. A loophole in the U.K. Human Fertilisation and Embryology Bill is that clinics offering only GIFT might not need to be registered, and at a practical level, there may be insufficient staff to monitor their operation if registered. The MRC interprets the bill to include GIFT, as it is a procedure that involves "an egg in the process of fertilisation" (Braude et al. 1990). GIFT is cheaper than IVF as it does not require laboratory maintenance of gametes or embryos. However, it is considered more risky by some experts (Vines 1990). Because the techniques are similar, if IVF is going to be regulated, GIFT should also be regulated, and statistics collected for study of these techniques which are still at an early stage in refinement.

There are several reasons why GIFT should also be regulated by committee

licensing. The maintenance of proper clinical standards is important, which can partly be measured by the statistical performance of each centre. The individual statistics need to be keep. In Australia and New Zealand most clinics offering IVF or GIFT send their annual results to a monitoring group, at the Australian National Perinatal Statistics Unit (PNSU 1990). It also shows the high variability between the performance rates of different clinics. There is a stronger need to monitor the incidence of multiple pregnancies in GIFT, as more eggs may be implanted, or not all the eggs were extracted so that some remain to add to the chances of multiple pregnancy when the egg and sperm are returned to the woman. There are many implications of multiple pregnancies, such as higher mortality rate, and social consequences for the family.

The claim that AIH or IVF are risky for the offspring, were important objections against the early use of these techniques. In hindsight, we can say that there is no significant additional risk of defect to children born as a result of IVF compared to those of normal conception (Edwards 1985). This was a valid objection to these techniques before their use, and some would consider that when they were first used they were unethical because of unknown risks. The spontaneous abortion rate after IVF and embryo transfer is not significantly different to that after natural reproduction, being about 40-60% at conception, and about 25% at two weeks gestation (Steer et al. 1989). There have been many multiple pregnancies as a result of IVF, but the reason for some has been the high number of embryos replanted. In a survey of the British IVF births up until 1987, out of 1092 deliveries, 249 were multiple births (23%), which compares to 1% for natural conceptions. The average birth weights were lower and there was a greater proportion of premature births because of this (MRC 1990). There is a slightly lower overall survival rate for babies born as a result of IVF because of the lower weight babies, due to the three times higher rate of multiple pregnancies. However, there has been no evidence that the procedure itself is harmful. If we control the incidence of multiple pregnancies than the procedure presents no known risks to the child.

Some regard IVF as "unnatural" because the embryo is conceived outside of the body. However, there is nothing intrinsically more unnatural in fertilisation in vitro than some other medical techniques. There may be other reasons to oppose IVF, such as its potential misuse, or the following arguments, but unnaturalness is not convincing.

The religious objections to masturbation used in these treatments are used only by a few conservatives, most theologians do not consider this important (BSR 1985). The motive behind the act of producing semen is procreative and so different to the acts that those claiming scriptural objection refer to. Religious taboos may be eased in the case of IVF, as it leads to cocreation of children. There are in fact social taboos on infertility which bring pressure and create problems for the couples seeking IVF treatment. The sexual taboos should not have a role in the assessment of these issues unless they are morally relevant. We should note that IVF for married couples is accepted in some Islamic countries, where there are clinics. It is also accepted by many Jews, and there are clinics in Israel, that will provide services to a broader group of infertile women.

There is still objection to the separation of procreative and conjugal aspects of marriage, from the Roman Catholic church (Vatican 1987, Stagnolo et al. 1989).

The view of the Roman Catholic church has been that aids to infertility involve the intrusion of a third party, the physicians and scientists, into the marriage as a means of solving the infertility problem. This was seen as a trepasses upon the covenant and exclusive relationship between the husband and wife, who are "one flesh", and also intruding into the parent-child relationship of the family. However, this is like the argument that medicine is unnatural, there is usually the involvement of a third party. The argument that children who are not born as a result of conjugal intercourse are deprived of "proper perfection" (Vatican 1987) has no scriptural, reasoned or scientific basis. This is not only an unscriptural doctrine but cruel, harmful and in my opinion a mistake which needs changing, as such statements affect the lives of many people, who look to religious authorities as sources of moral guidance. We can hope that theological intepretations consider new technology.

In Japan there has been a survey of the attitudes of Buddhist Priests towards new reproductive technology (Shirai 1990). Among the Japanese population in general, about 30% of the general population approve of IVF, and 55% disapproved, in a study at the end of 1985. A group of Buddhist priests and student priests was surveyed, from several different sects. About 43% of the respondents approved of IVF in the case of a married couple, and the major reason was the sympathy for the infertile couple. Only 22% disagreed with the procedure, the survey was conducted in early 1987. These figures suggest that the Buddhist monks are more accepting of the use of IVF, though it may also be a partial reflection of the growing acceptance of new technology within a society once it is used. The main objection to IVF was it is interfering with nature, which is the argument discussed in chapter 3. These attitude survey does not necessarily reflect much theological reflection, as there has been very little theological examination of this technology by Buddhist scholars.

In the simple case of the use of these techniques for a married couple, there is no relation to the "brave new world" situation. The use of these techniques supports the traditional family values. Human life needs an environment of love to flourish, and this love can be provided in the marriage to a child born in any way, and probably more so towards a child that involved much difficulty to be born. The procedure of IVF has raised the question about intercourse being not simply a biological event, but a symbolic human event expressing human love. A woman who is able to conceive does not necessarily mean that she is able to procreate. There may be problems in the conflicts of interest, but these are more important when extramarital gametes are used.

There are associated legal problems that require regulation. These include who has legal control over gametes and embryos, and who decides their fate. The primary authority should rest with the two gamete providers, who should agree to any disposition of the embryos. Agreements made by the gamete providers for the future disposition of the embryos should be enforceable to avoid problems arising from divorce cases. There has been an infamous case in the USA, called the Davis case, where the couple divorced. The woman wanted to use the frozen embryos to try to become pregnant, but the man wanted to prevent this. A Tennessee court supported the woman's claim, but it is being appealled. It is best to have these legal questions decided, and an agreement entered before starting IVF treatment. In light of past legal problems many clinics have developed detailed consent and instruction forms. However, it is not an objection to IVF itself, and is a manageable problem.

The moral status of the embryo is an important question, as some embryos may be discarded if not all are used in IVF. I considered the moral status of the human embryo in chapter 5. The conclusion was to support the use of human embryos in scientific research for important medical goals, and to improve the success rate of IVF. The technique involves making spare embryos, which may be used at a later time. There is a high level of embryo wastage associated with natural fertilisation, about 70%. There are large numbers of gametes unused, far more than is necessary for reproduction. The embryos are only 1-4 cells in size. If just one child is made from four embryos then we have the same situation as in nature, and in my opinion it does not matter if the figure is 20 to 1 at this stage of development. Rather than looking at the embryos wasted, we should focus on the utilisation of gametes that would otherwise have been unused, and more importantly, on the birth of a child that would not have been possible without using this technique.

Spare embryos can be frozen, and used for another attempt at embryo transfer, and this is routine in some clinics. To lower the risk of multiple pregnancy only three embryos are usually transferred per attempt. Freezing avoids wasting the embryos, and the survival rate for embryos is greater than for oocytes. It avoids the need for oocyte recovery from the mother before every attempt. It has not been found to be associated with any risks to the child. It does present several important ethical and legal issues, after the couple have a successful live birth, on the disposal of the frozen embryos (as well as the disposal of unused sperm and oocytes). The embryos may be used for a future attempt by the donor couple, or they may be donated, or discarded, or used for research prior to discarding. In practise most clinics follow the wishes of the parents.

There have been objections from the feminist movement, who claim that IVF is a failed technology (Arditti et al. 1988). Their opposition to reproductive technology is based on the hypotheses that it reinforces social attitudes concerning the imperative of biological parenthood (with the stereotype of women as child raisers); it increases the possibility of exploitation of women; there are possibilities such as sex selection (which is often based on a low value of female over male); the commercialisation of gametes, embryos and women, so they are viewed as commodities; and the experimental nature of the techniques. It is true that IVF has a low success rate, but it still is successful, what is imperative is that there is better counseling and prior knowledge of the low success rate, as many unsuccessful couples find it emotionally draining. It is very important that infertility is seen to be one factor in life, and the birth of children is not required to live a full life. This objection to IVF is more important than most of the philosophical arguments about the status of the human preembryo in relation to reproductive technology. The exploitation and commercialisation of these techniques are discussed in the following pages.

The objections from several feminist writers have however, highlighted the severe emotional stress that couples and especially women undergo when using these techniques (Frank & Vogel 1988). They also criticise the businesses that are making money out of offering this technology, such as surrogate mothering agencies. This may place increasing pressure on people to have children, whereas in the past they accepted their conditions. There is a certain peer pressure to use new reproductive technology if a couple is infertile, even if they would not have gone through the stress or financial cost, without this pressure to conform.

In an overpopulated world there is something incongruous about using all the ingenuity of modern medicine to create more children. However, it is not an ideal world. Most of us are free to adopt needy children, from our own country or others. If fertile couples don't chose adoption in addition to having their own, we can't enforce things on others, especially what we don't do ourselves (Jones 1985). "Infertile" couples may have to consider the option of adoption more than couples who are easily able to have children. There is a strong desire among couples who are unable to have children to use these techniques, but in one survey of patients involved in IVF programmes 70% of the couples using IVF would use adoption or AID/IVF using extramarital gametes, if those possibilities were available (Singer & Wells 1984). Unfortunately, there is a shortage of children available for adoption, unless international adoptions across cultures and races are accepted.

Should IVF be Publicly Funded

By todays standards IVF is not an inordinately expensive medical technique. As mentioned in the section discussing whether infertility is a disease, reproductive rights are involved. It is one thing to recognise the right to treatment, a liberty right; but another to recognise an entitlement right, the right to expect society to pay. Infertility treatment could be regarded in the same way as other medical therapy, and different countries provide national health schemes, and others do not. Some ask whether it should be included in the range of treatments subsidised from community medical resources. There does not seem to be any reason to single IVF out for harsher treatment than given to many medical treatments. We still treat lung cancer caused by over smoking, liver disease caused by alcohol abuse, or heart attacks caused by bad eating habits, on national health schemes, or under medical insurance schemes. In fact, one would favour the motives of IVF over some of the other treatments possible. IVF only benefits a small proportion of infertile couples. The real cost of the IVF and embryo transfer procedures alone per live birth is A$ 40,000 in Australia, and US$ 50,000 in the United States (Wagner & St. Clair 1989). There may be more cost effective ways to treat infertility, and further research is needed. About 15-25% of couples waiting for IVF, or failing IVF, have pregnancies before receiving treatment, or within two years of its discontinuation. Research may lead to better alternatives.

Nevertheless it does highlight the wrong in the world that we invest resources in order to help a few thousand childless homes get a genetically related baby, when we don't simultaneously invest the same resources to help the millions in developing countries be able to live, and overcome the tragically high rate of infant mortality. We also have to decide whether IVF is consistent with the ultimate aims of medicine, the restoration to health of those diseased and impaired. Some believe it is more towards the satisfaction of other needs, for which there is only a strong desire (Iglesias 1984), however, I do believe it is at least as worthy as many other medical treatments we readily accept.

In some countries IVF is performed for a high fee, but in others it is covered by national health systems. A recent international survey was conducted by (Gunning 1990). In France IVF is fully reimbursed by Social Security, as France has a pronatalist policy. Some patients have to pay laboratory charges (about FF 2,500). In Spain 14 of the 24 clinics are in public hospitals where treatment is available in the National Health Service, and in private clinics the women can claim

on medical insurance. In Denmark there are six clinics offering IVF, five of them are in the National Health Service Hospitals and offer free treatment, under strict criteria. In Italy the state will reimburse the costs of IVF with gametes from the married couple, but in Sicily the government will also reimburse the costs of IVF using donated gametes. In Belgium the social security system will contribute to the cost. In Norway the state pays 90% of the cost, and IVF and AID may only be performed in authorised institutions included in the national or county health plans. In Canada, public health funding is on a provincial basis and Ontario is the only province which covers the cost of IVF. British Columbia has withdrawn financial support for IVF. In the Netherlands some funding is available from the Sick Funds Council, but it is still a matter of debate whether it will cover future IVF treatments. Private medical insurance will meet IVF costs for those not covered. In Switzerland IVF services can be performed at approved private institutions.

In Britain only two clinics offer free service under the National Health Service. The charges at the other clinics range from 250 to 2000 pounds. In Australia approximately half the costs are available on Medicare, so patients pay A$ 1-2,000. In the USA couples pay on medical insurance cover, and six states (Arkansas, Delaware, Hawaii, Maryland, Massachussetts & Texas) have mandated medical insurance cover. There is a varying degree of coverage under state Medicaid programs, with some cover for drugs, counseling and surgical procedures related to infertility treatment, but no direct funding of IVF (OTA 1988c). In West Germany medical insurance will pay. In Sweden patients must pay the costs (between US$ 3-4,500) (Gunning 1990).

Eligibility

In principle IVF and artificial insemination are accepted means to aid infertility to married partners, using semen or eggs within the marriage, by most Christians (Mahoney 1984), and also in some cases by Jews (Jakobovits 1975). The possible consequentual uses of human embryos, especially fears of genetic manipulation raise many additional moral concerns, which are a separate issue, are described later.

There is the question of whether prospective parents should be screened for their suitability to have children. Assisting single parents or homosexual couples to conceive a child may directly contribute to specific negative child-rearing conditions in most cultures. This may harm individuals and also the wider community. There has been some evidence that children from single-parent households do not do as well academically as children from two-parent households (Orentlicher 1989). However, this may reflect differences in income, education and other factors. Some other studies do not find differences in academic performance among children depending on the number of parents. Girls who have a single mother may be more independent and more achievement orientated (McGuire 1985). In some instances the child may be raised in a better environment than children in heterosexual families. There are also a large number of single parent families existing in Western countries, because of high divorce rates, and premarital pregnancy. What is important is that active intervention in bringing about the birth of a child is involved. Society can try to increase the number of ideal family situations by marriage counseling, and it is a backward, even if minor, step to use technology to generate unusual family situations. Normally people are not screened if they will be good

parents, only if they commit child abuse are their children taken away. There might be cases where a heterosexual couple is "judged" to be unsuitable for nonmedical reasons for IVF, in which cases they should be told why, honestly, and then they can seek the services of another doctor.

The Council of Europe adhoc Committee on Bioethics prepares drafts for the European Committee of Ministers. It recommended that the techniques of artificial procreation should be restricted to heterosexual couples (Gunning 1990). People in Norway must sign a declaration that they are married. In Sweden the recipients must be married or cohabitants for more than two years. In South Australia IVF is allowed only for married couples, or for couples with at least five years of continuous cohabitation. However, in Spain the law makes reproductive services (IVF, GIFT, AIH, AID) open to any woman, whether married or not. In Israel an unmarried woman can receive IVF with her own fertilised ovum if a social worker in the clinic supports her application.

In the U.K. Human Fertilisation and Embryology Bill there is a conscience clause for the medical practitioners which states "No person who has a conscientious objection to participating in any activity governed by this Act shall be under any duty, however arising, to do so". The Bill makes reproductive services generally available for "the purpose of assisting women to carry children". On clinical indications alone, services are open to any women. However, the conscience clause allows doctors who have a genuine conscientious objection in the interests of the prospective child, to refuse services. The burden of proof for the objection still rests on the practitioner (Evans 1990). This still allows some selectivity, but it is likely that a sympathetic doctor may be found to provide the services. On the more sinister side, it may force the rejected women to use more expensive services than if there was an open policy.

The eligibility for using reproductive technologies is an important area of the law. While the resources are limited, they should be solely applied to benefit infertile married couples. For longterm de facto "married" couples, who wish to have a child by IVF, it would seem that they should be prepared to become legally married if they wish to use the involved procedures of IVF, and to raise children. There are IVF clinics practising in Egypt, Jordan, Kuwait and Saudi Arabia, and only their own gametes are being used. However, there is no legislation controlling IVF, and there may be many unofficial clinics. In West Germany, IVF can only be used for married couples, which is a contrast to the situation in the Netherlands where lesbian couples have used IVF and AID. In the USA, courts have ruled that it is not possible for clinics to refuse to consider applications for reproductive technology from unmarried couples, or single women. In the U.S. Constitutional tradition, there is a right to procreate and raise children according to individual preferences.

Fertile people may have a need for infertility treatments also. People who undergo radiation treatment, especially women, may want to store eggs for use after. Some chemotherapy agents also can cause mutations. Treatment for lymphoma can use gonadotrophin alkylating agents which cause premature ovarian failure in most women. Oocyte recovery would allow future pregnancy. A women in the twenties may want to store oocytes produced then, for implantation in the thirties when she wants to have a child, as older women have increased risks of chromosomal abnormality (Dawson & Singer 1990). Abnormalities can be screened

Table 11-1: International Comparisons of In Vitro Fertilisation (Information from ANPU 1990, Gunning 1990, ILA 1990, Mori 1988)

Nation	Legislation	Embryo Research, Time Limit (days)	Regulatory Body	Number of Clinics providing IVF	Treatment Cycles p.a. (Live birth rate %)
Australia & New Zealand	Victoria 1984, and South Australia 1989	Surplus, (14)	Standing Review & Advisory Com.	25 (1988) 3 in N.Z.	9,191 (9.4)
Belgium	No	Yes (no restriction)	No	14	Unknown
Canada	No	Yes (no restriction)	No	13	2000+
Denmark	Establishing National Bioethics Council	Moratorium on all research	No	3	900
France	Draft 1989	Surplus (7)	National Com. licenses clinic	>100	19000 (FIVNAT)
F.D.R.	Bill 1990	No (5 year prison)	Yes	51	14,400 egg collections
Italy	No	Yes (no restriction)	No	10+	Unknown
Japan	No	-	No	<45(1986)	2008 (6%)
Netherlands	No	Yes	No	30	2377
Norway	Act No. 628 1987	No	No	7	3-4,000
Spain	Law 35 1988	Surplus (14)	National Commission	24 (1989)	2500(1989)
Sweden	IVF Act 1988	(14)	No		
U.K. Up to 14 days Licensing Authority	Human Fertilisation & Embryology Act 1990	Yes (14)	Licensing Authority	44(1987)	7043
U.S.A.	No Federal Legislation In some states yes.	In some states yes, no federal funding	No	200	14619 (in 146 clinics)

for using genetic screening, but oocyte recovery when there is a more significant risk of mutation, and the case of possible absence of oocytes, is justifiable. It is a question of resources available, more than anything else, once we accept IVF as an ethical technique.

The Use of Extramarital Gametes

Sometimes one member of a couple may be incapable of producing gametes which can lead to fertilisation, so that IVF or AIH will not work. The couple may not be infertile, but one may carry a genetic defect and so would not like to take the chance that the offspring also suffer from that genetic disease. If these couples do not consider adoption a possible option and still want to have children, then they

may consider use of artificial insemination using donated semen (AID) or IVF where the egg, or sperm, may come from another person. In about 30% of infertile couples, the male alone is responsible for the couple's infertility.

The first documented human insemination using semen from a husband was performed by John Hunter in London in the 1770's. The oldest claimed case of medically assisted AID was in 1884, but it was seldom used until the later half of this century. The success rate per patient after three months is about 40%. In the United Kingdom about 1700 children a year are registered born as a result of AID (H.M.G. 1986), and they were legally regarded as illegitimate until the 1990 Human Fertilisation and Embryology Bill was passed. About one in 20 of the British population today, has a father other than the one named on the birth certificate. In the United States the number of children born by AID is measured in hundreds of thousands, and about 30,000 children are born annually (OTA 1988c).

In Europe the situation varies between countries very widely. In France there are about 20 centres that are regulated by the Ministry of Health.CEGOS sperm banks; They have developed a set of guidelines in the use of semen. Semen is obtained only from married fathers, with the approval of the spouses. There is a high demand for sperm, and a limit of 5 pregnancies per sperm donor (Jalbert et al. 1989). Anonymity of donors is guarantied, and only stable heterosexual couples are recipients. The recipient cannot chose a donor, and they must have a medical reason for using AID. There is no payment for sperm, though it has been shown that payment encourages more donations, but sufficient sperm is obtained from donations (Glover et al. 1989). More than 17,000 children have been born in France as a result of AID, and 0.25% of births in France are a result of CEGOS services. There are continuing followup studies, and the scheme has been running for fifteen years. There is a greater openness about infertility in France than in some other countries. In Denmark, AID is prohibited (Gunning 1990). West Germany discourages AID, and the new Bill prohibits egg or embryo donation.

In Sweden usually married donors are used, and when the child is 18 years old they can obtain the name of the sperm donor. Only married couples (or long term defacto couples) can use AID. When the law removing anonymity was introduced there was an initial drop in the number of sperm donors, but since then numbers have returned to an adequate level. The written consent of the woman's husband or cohabitant is required, and AID must be performed in a public hospital under specialist supervision. A couple may appeal to the National Board of Health and Welfare if their application for AID is refused. The doctor selects an appropriate sperm donor. Frozen sperm are prohibited from entering Sweden. However, many Swedish couples seek AID in countries where anonymity is guaranteed. The Swedish law prohibits the donation of eggs or embryos for IVF. In Bulgaria the written consent of the husband is required prior to AID, and only if the couple cannot have children with their own gametes or the husband suffers from a serious genetic disease. Donor sperm must be from donors between 18-40 years of age, and is screened for infectious diseases (Bulgaria 1987). In South Africa the written consent of the husband is also required, and only married couples can use AID.

In ethical terms I consider AID and embryo donation to be equivalent, the only difference being that the embryo is conceived in vitro in one case. In fact the embryo can even be fertilised in utero, using GIFT, or transferred after fertilisation by embryo flushing. The women can be inseminated with the semen of the infertile

woman's husband, then after a brief incubation in vivo, the embryo(s) are flushed from her body and replanted in the infertile woman. The donor mother can be made to superovulate by hormonal treatment so more embryos are produced. The use of IVF may seem more preferable than flushing, as it means less involvement for the egg donor in the process, and IVF is a relatively efficient, safe technique.

The intrusion of a third party into the marriage is genetic as well as physical in these cases (Dunstan 1975). The involvement of a third party is the crucial objection to AID seen by many (O'Donovan 1984). The biological imbalance introduced into the parent-child relationship is an additional factor to the possible resultant stress between the husband and wife about the child (Snowden & Mitchell 1983). The asymmetrical genetic relationship of the child with the parents is a main concern. There is very little evidence of the actual results as the process has always been kept secret. It may have a close parallel to second marriages to which one partner may bring children of a previous marriage (Mahoney 1984), though the parent-child bond will be closer because both parents were involved in the pregnancy, birth and raising of the child. Since there are many instances of successful and loving marriages, in these categories, it seems acceptable for a stable marriage to use AID or IVF on this criteria. In fact, in France couples who have children by AID have only a 2% divorce rate, lower than the general population. However, in these situations the child exists, but AID involves deliberate conception of a child into an unusual family situation.

The considerations about the child are of paramount importance. A child needs a secure and loving environment to grow well. Children may also want to know their origins, and may have the right to know their biological parents. There has been one major study published that indicated that the majority of couples who used AID were very happy for the children that came as a result, and had no regrets. Both husbands and wives had found parenting rewarding and were happy with their children, after a long period. The children that knew that they had come from using AID were also happy (Snowden et al. 1983). In France studies so far have shown that children are not at any psychological disadvantage. Further studies should be done, such as the reactions of couples who use AID but do not have children, but their is much weight to social studies such as this if the answer is clearly positive. It is difficult to study as many doctors do not keep records of AID, and even if they do it is secret. It may be important to use criteria that something is morally wrong on grounds other than the consequences to which it will lead. The consequences vary with different marriage situations, and you can not tell necessarily which couple will make the best family situation.

A reason for objecting on religious grounds is that it may break the exclusive covenant relationship which God has established with each married couple. It is the closest of personal unions, which may mirror the union between Christ and His church. In this closest of personal unions, new human beings are brought into existence, as the fruit of God's creative love, and of the co-creative mutual love of husband and wife (Mahoney 1984). But it is an imperfect world, and not every family has great love shown in it. AID is not marriage infidelity, as it does not involve an intimate relation offending marital fidelity. However, AID is generally condemned by many Christians and Jews. This is in contrast to adoption which is considered ethical, except in Islamic countries. AID is grounds for divorce under Islamic law (Schenker 1985). There are IVF clinics in a variety of Islamic

countries, and no gamete or embryo donation is permitted in these clinics, and there use is only for married couples.

The two sources of extramarital gametes that are commonly used are those donated by relatives or friends, or those from completely anonymous sources. Because of the risk of a conflict of attitude toward an offspring from an identifiable nonparental source, anonymous donations are prefered. In fact, recently in the United Kingdom the Voluntary Licensing Authority that licenses centres carrying out IVF and embryo research (set up after the M.R.C. report after the Warnock Committee report by the M.R.C.) made guidelines, which include that no more than 4 embryos should be replanted at one time and that donor gametes should be from anonymous sources. The reason given for anonymity was that this is best in the interests of the children. In fact it is probably more that it it is the best interests of the donors, who are often medical students, who have no connection with the parents. They would get a great shock to have a teenager coming to them 20 years later saying "Hello Father". The British Medical Association in 1970 recommended that the procedure remain anonymous. Also many Asian and Muslim mothers seek AID without telling the husbands, as it is not understood that the reason for infertility can also be the males fault!

In actual fact it is very difficult to conceal the fact, and will become much more difficult in years to come when genetic fingerprints of many people start to be recorded. In Sweden the child can find the identity of the genetic parents, like adopted children. In the U.K. the information of the identity and characteristics of the donors will be stored by the licensing authority for up to fifty years in some cases. Details can be divulged to the children concerned in limited circumstances (HMG 1990). The actual identity of the donors will not be disclosed, unless the Secretary of State for Health alters the information to be provided. This reflects the idea that the public opinion may change, as in the case of adoption (Evans 1990).

The issue of anonymity is very contentious, as some would say that if the parents do not tell their children that they are not their genetic parents, it is always going to be a deceitful relationship. Many children never know their origin. We need to question which is greater, the desire of the resultant child to know their genetic parents, or the desire of donors to retain anonymity. It is claimed that if donors know that they might be traced, they would not donate gametes and this would result in a shortage of donors, however as mentioned, in Sweden there are still sufficient donors. We need to change society's attitude to the importance of genetic ancestry. In 29 states of the USA there are AID laws that name the recipient and her husband as the legal parents, and that the sperm donor is not the legal father (Hummel & Talbert 1990). The legal definition of parents should be changed, as has been done in Britain. However, the U.K. Bill is still backward if it maintains the anonymity of donors despite the needs of the prospective children. It is currently unclear what information about gamete donors a child will be able to obtain. In the early stages of the Bill the wording was to release "non-identifying" information only, but in the Bill this phrase "non-identifying" has been removed, so potentially any information is releasible. Like adoption, when the child reaches a certain age they should have access to the records of who the biological parents were,though the legal parents are those who raised the child. In Britain adopted children only have direct access to who the birth mother was, and about 5% of the children have used this provision (Braude et al. 1990).

Besides the ethical argument that children should be able to know their roots, there are also medical reasons for regulation. This is especially so for semen donors, as there has been numerous accounts of the transmission of infectious diseases, such as HIV, ureaplasma, cytomegalovirus and herpes simplex virus. There is currently a lack of systematic screening of semen (Barratt & Cooke 1989), though some AID programs involve screening for many viruses (Hummel & Talbert 1990). It has been found that the same success rate is obtainable using frozen semen as with fresh semen (Scott et. al. 1990). In France there is some genetic screening of semen, and recipients, to avoid known serious genetic disease (Jalbert et al. 1989). The American Fertility Society 1990 guidelines (AFS 1990) recommend that fresh semen should no longer be used for donor insemination, and that all frozen specimens be quarantined for 180 days and that the donor be retested to ensure no antibodies to HIV are found, before releasing the specimen. They also recommend that each donor should be limited to 15 successful pregnancies, though less in smaller local areas. In South Africa the maximum number of children that one donor's sperm can be used for, is five.

However, in the final analysis it is impossible to enforce regulations on AID as it can be self-administered. In 1979 the Council of Europe recommended that all non-medical performance of AID should be unlawful, but the member states of the Council did not accept this for reasons relating to the practicality of such a law. It is not possible to regulate, and even if it may be detected during childhood by DNA Fingerprinting, it is undesirable to make the child "illegal" in some way.

It may be more balanced to use both egg and sperm from outside of the marriage, making the separation between genetic and social parenthood more fully. Donated embryos may be used, it is generally considered that any "spare" embryos made during the process of IVF, or donated egg and sperm, remain the property of the donors. The responsibility of safe medical practise is the responsibility of the medical staff. The doctor used to be the major selector of donors, but with the existence of large sperm banks the parents can increasingly chose the donor's characteristics, usually to match those of the husband or possibly with eugenic aims. There needs to be control over the number of times the same donor is used, so that there is a low chance of unwitting incestuous marriages. Some believe that the procedure is best left under the control of doctors, but it is very open to personal abuse.

There are commercial sperm banks operating in the USA, which has long been tolerated but is widely considered to be unethical. In the U.K. payment to gamete donors is prohibited, as is payment by the recipients to donors (HMG 1990). There has been a study conducted in Paris which showed that payment encourages donation (Glover et al. 1989), but there should still be adequate supplies of semen without this.

In the case of some dissatisfaction with the procedure's results, such that the parents have a disabled child or multiple births, providing the procedures have been explained to the parents and followed, there should not be grounds for lawsuits against the doctors, as has already occured in some cases. These techniques do not appear to have significant risks attached, monitoring them is the only way to investigate their safety.

There does need to be some regulating laws, but it is a case for situation ethics. There are widely variant laws in different countries, which is a consequence

of the difficult issues involved. Society's attitudes to the use of donor gametes affects the legal controls, and if society grows to be more openly favourable to AID it will make regulation easier. It is impossible to prevent some abuse as AID requires no sophisticated technology, so it is best to allow it in a regulated way.

Surrogacy

Biomedical technology has made it possible for over a dozen new modes of reproduction. A child can have up to three types of mothers (genetic, gestational and social) and up to two types of fathers (genetic and social). It is possible to separate both genetic and social parenthood from physiological parenthood, as in the case of womb-leasing, or surrogate mothers. There already are children born, at least 500 in the USA alone, and reintroduced with their genetic parents, who will become the social parents, after birth from surrogate mothers. There are laws in Britain, and some other countries including Bulgaria and some states of the United States, which say that if the surrogate decides to keep the baby than no contract that she has signed can prevent her doing so. Carrying a baby to birth is the primary legal right to being a parent of the baby. In other countries, such as Greece, the Netherlands, Portugal, and Czechoslovakia, and thirty states of the United States, the preconception intent of the parents governs who are the legal parents of the child born (Andrews 1988). It is doubtful whether surrogacy should itself be illegal, as it seems strange to make the birth of a child illegal (Glover et al. 1989). However, it should still be strongly discouraged.

There are psychological and emotional factors which require careful scrutiny. Surrogacy in terms of financial gain is morally wrong to most people, and commercial surrogacy is illegal in Britain. In Australia the National Bioethics Consultative Committee recommended in August 1990 that surrogacy should be permissible in certain circumstances. In the state of Queensland surrogacy is legally prohibited, but the committee considers the factors that it is impossible to prevent it occuring and it is better to regulate the practise. It is still developing the working guidelines, and would make all surrogacy contracts unenforceable.

Surrogacy could lead to the situation where wealthy couples do not have to have the experience of pregnancy but let other women, who need money, have the troubles of pregnancy. There is a real danger that it would lead to the exploitation of poorer women. In the United States there are many surrogacy agencies, which involve commercial payments. A list of these agencies can be found in an appendix by a book by Evans (1989), that considers some of the excesses of reproductive technology in modern medicine. The total fee of most agencies is over US$20,000, up to half of which may be an agency fee. It is not the same as adoption, as adoption is finding a home for a child that exists that does not have a home, it is serving the child's interests. In surrogacy, or AID, the child is not being adopted, it is being created as a product to satisfy the desire of the parents. It is not done for the best of the child, but for the sake of the parents. It is a very short distance from the situation where children are viewed as consumer products, to add to the nice car and home. This is a concern seen especially in these treatments for infertility that involve multiple parties, and start to use people as means, and involve financial costs. It may also be considered desirable by some women who consider pregnancy to be an obstacle to their careers, in this case it seems unlikely they would provide a proper living environment for children anyway. There are both physical and emotional

risks in having a pregnancy, and it is generally viewed as unacceptable because of the possible harm to the mother. I would view commercial surrogacy as unethical and something to be legislated against.

However, the offer of physiological motherhood by a sister or friend to a childless couple, could be treated as a generous offer (like the arguments used in allowing tissue donation). It is a novel concept, but novelty is not an indication of moral wrongness (Mahoney 1984). In this case it requires more careful examination, and might not cause many problems in the best case. In the U.K. however, no surrogacy is currently recommended with close relatives (VLA 1989). The legal concepts of mother and father have been changed in the U.K. so that the women who carries the child is to be the mother and her husband is to be treated as the father, unless it is shown that he did not consent to his wife's treatment (HMG 1990). This legal clarity is not seen in many countries.

A fear from many feminist writers is that the new technology is another control over women's lives at a new level (Arditti et al. 1988, Klein 1989). However, there have always been dangers of exploiting the fact that women carry the fetus, and any new technology involving reproduction is going to involve them. While contraception has freed women of the need to have so many pregnancies, techniques for relief of infertility are usually sort at the wishes of both members of the couple. There is a certain attitude that women have to have a child to please their husbands, but this is certainly nothing new. If anything women should be pleased with the development of safe contraceptives, and there will be some experimentation while any new drug is developed. Certainly western countries should not use the third world as a testing ground for drugs because of stricter laws in their own country, but that applies to all people who are victims of unethical trials. The only technique which is particularly prone to exploitation of poorer women is that of surrogacy, which in fact is accepted more in the so-called liberal USA, than in traditional countries in Europe.

Avoid Risks of Harm to Children

It is improbable that ectogenesis, the growth of the fetus outside the human body will ever be possible for the whole period of fetal life. It may be useful in the case of an immunological rejection of the fetus by the mother, so there is a case for development of emergency procedures, but the use of immunorepressive drug therapy is a safer procedure to consider. Although ectogenesis is scientifically far away, as the problem of imitating the placenta is very difficult to overcome, it is not impossible. There is research in this area, one of the medical uses is to help babies from premature births develop (babies born at 6 months have been raised, which otherwise would have died). However, the unknown affects of total embryonic development outside the body, on the growing individual is too great an experiment to ever justify. In the more general application of alleviating discomfort of pregnancy, the similar principle used to the case of financially paid surrogacy could be used, that if the parents are not prepared to experience pregnancy they may not be prepared to make the necessary sacrifices during the child's life.

Edwards (1984) has suggested that making identical human twins could be of value as twin transfers give higher rates of implantation than single transfers. When it is only possible to obtain a single embryo from collecting eggs, it would increase the chances of a pregnancy if that embryo was split. Animal studies would suggest

that making 2-4 embryos from one, would present no extra harm to the babies born. Skills in human embryo manipulation are improving, and preimplantation genetic biopsy is possible. It has probably been technically possible for several years. The efficiency of IVF could be increased by about 50% if this could be used, on the basis of current animal studies (Wood 1988). Most of the main IVF clinics have purchased micromanipulators by 1989, this sort of splitting is technically possible in a growing number of clinics. The Council of Europe (1986) has recommended that even the creation of identical twins after IVF by embryo splitting, which would appear to present little harm in view of the limited animal studies done, should be forbidden. It might be too hasty to introduce a law which would ban embryo splitting. The question of genetic manipulation is considered in the following chapters.

The work with embryonic stem (ES) cells on humans is more dubious, however, if conducted within the time and developmental limits for human embryo experimentation there is some case for it. In this case chimeras could be made by mixing cells from several sources, like those made in mice for over twenty years. If we are prepared to justify some human embryo experiments for their scientific or medical benefit, then this class could also be reviewed by the regulatory authorities, in light of the fact that genetic manipulation can yield much scientific information, and the major interest in the roles of genes in development. We could imagine some longterm extrapolation to use for corrective germline gene therapy on humans, however these experiments could only be justifiable by use of what seems now to be unethical trials, which the first subjects would be. The affects of being a chimera are unknown, and if it is found acceptable to use germline gene therapy, an alternative may be better. It may be best to wait until other techniques are developed.

The important point would be never to risk harm to a baby being born. There is probably little risk to the mother. This is the reason why abnormal embryos detected by IVF are never implanted back into a mother; the child may be disabled as a result of the manipulation. There also has to be questions asked about the limits of using gametes from parents who are extremely infertile. The children will also inherit the defect, and be infertile, using special technology will propagate the disorder. There has to be a limit to the extent to which people want their children to be genetically related. It may be better to implant embryos from donated, fertile donors, of normally reproducing parents, if the patients still want to bear a child. The same argument that says that procreation is not the primary purpose of marriage and argues for the use of contraception, can also argue against types of treatment for infertility, especially those requiring excessive manipulation to achieve fertilisation.

Changing Family Structure

The case of separating genetic parenthood from social parenthood, is highlighted more in the use of egg and sperm to have a child in an extramarital relationship. The institution of marriage and a heterosexual family do continue to provide the most favourable circumstances for the loving environment needed to nurture a new human life. There are examples of longterm homosexual partnerships, which are loving towards each other. Some lesbian couples have

children by the use of IVF. The legal right to procreate is held by individuals, not by couples, but this is not the same as a right to have offspring by any means. Sexual intercourse outside is grounds for divorce. Multiple marriages are illegal in most countries, as is consumer surrogacy. The use of AID by unmarried women should not be condoned, despite the ease in our society of women having children outside of marriage. As previously mentioned, society should not encourage this type of single parent family.

There have been major differences between the ages at which people get married, and the size of the family living together. There are similarities and differences across cultural and religious boundaries. For example the Japanese family group is often three generational with a senior married couple and a junior married couple, and the unmarried offspring of both, which is similar to that of the Basque region of Spain. The average age of marriage varies, for instance in China last century it was about 17 years for women, but in Japan it was 24 years generally. There were wide regional variations. The Chinese used to marry early, but during the last three decades the government has tried to delay marriage for about ten years, which can be a major influence on the family size. In China only female infanticide was practised, and all males were welcome, but in Japan the number of males was also controlled by infanticide or abortion. Also in Japan, marriage at later age has also been used in the past to control the number of children in poorer economic conditions. In Western Europe fertility was controlled by a combination of late marriage and celibacy (Hanley & Wolf 1985).

Adoption has been practised in many ways. For instance in one study of a certain social class in northern Taiwan it was found that between 1906-1915 70% of the girls born were given out in adoption as prospective daughters-in-law to the home of their future parents (of these about 45% actually married the son of the family). Children living together as brother and sister often develop mutual sexual aversion, they had a higher divorce rate and a lower birth rate than "adult" marriages. To test the sexual attractiveness the couple were encouraged to try out before marriage, the proof of which was pregnancy, hence there was a high premarital pregnancy rate (Sa 1985).

Multiple marriages have been observed in a number of cultures, for a variety of reasons. Polygamy was common in most of the world, usually one man with several wives, though sometimes such as in some Himalayan societies a man shares his wife with a brother, who has a second wife also. In Eskimo culture a man will share his wife with business associates as a sign of hospitality. However, in those societies it was not the exclusive form of marriage and many men lived in monogamy because of a limited number of women and limited finance. There were several advantages for the male; the economic contributions of the many wives to household wealth, sexual companionship, and increased social status to the head of a large household. In societies where there is low regard for unmarried women it is also an advantage for the women, and they could share household labours with other wives. Usually one wife is senior, but not always, and often the wives had separate living room with their children. In Islam the number of simultaneous wives is limited to four, and while it was easy for a male to divorce, the detailed laws of inheritance led to a centralised family. In the Mormon church, the practise of polygamy was limited to an elite group, usually about 10% of the males last century. Although it was made illegal in the USA, there are some isolated groups still

practising it. The children of the lower ranked wives, or concubines, were given equal status to those of the senior wife in cultures such as Biblical Jews and the Chinese. In Tokugawa period in Japan between 1500-1800 it was found that some of the daughters of upper class Bannerman (Samurai class) decided to become second or third wives of the same socioeconomic class, prefering this class than to have to marry downwards in social status (Yamamura 1985). In developing countries polygamy is increasingly becoming unfeasible because of economic changes, urbinisation and mass education. There is a general prestige given to Western ways and to the feminist movement.

The divorce rate also greatly varied. It varied in the time period of countries, for instance in Japan in Tokugawa in 1500-1800 it was 5-6% (Yamamura 1985), whereas in one study in another city, of Takayama during 1700-1800 the rate was 25%. In some countries it is very liberal, so that often couples can be remarried again, such as among the Bemba of Zambia, to countries where it is illegal such as in the Republic of Ireland.

One of the common grounds for ending marriage has been sterility, the failure of the marriage to produce children. In Jewish religious teaching after 5 years if there are no children it is grounds for divorce (Jakobovits 1959). In other countries the fertility is assessed more specifically in terms of whether any sons are born, the sexist thinking behind this is still prevalent in much of the world. In the New Testament of the Bible there is no such teaching, and the marriage was not seen as solely a procreative partnership but concentrated much more on the companionship offered.

There have been many changes to family structure in the past century, all over the world, and the process continues. Some of the change is for the good and other for the worse. This partly depends on what the family structure was like, or is like. Much more of the world is accepting a similar concept of marriage, of an ideal family being a heterosexual couple in a monogamous marriage for life. This concept is found in many countries under many religious systems, particularly that of the Christian belief. However, in the Muslim world several wives are still accepted in many countries, and even more in some African countries.

Family structure and the status of the family has often varied during history, even in the same culture. During reformation Europe it is estimated that 20 percent of women were spinsters and 20 percent widows, and that up to half the children died before the age of five (Ozmont 1983). The Reformers believed that the medieval church enforced virginity on unwilling youths, with exaggerated clerical ideals of virginity and celibacy. The church also had arbitrarily controlled the permissibility of marriages, which the Protestants saw as wrong. The model of the ideal was to be a monogamous marriage with the wife at home with the children, but studies suggest their was often little genuine affection between spouses, and between children and parents. However, marriage stabilised both individuals and society as a whole.

During the last century, there have been major changes in Europe, and these are still to fully spread throughout the world. The major introductions have been the rise of the divorce rates, which means that the family is no longer as stable as it is, and the availability of contraception to control the number of children. With contraception there are fewer children, which means that the mothers could have more time to start to pursue alternative vocations instead of being tied to the home,

and the father was no longer the sole bread winner so lost some of the paternalistic authority. It also meant that there was less danger from extramarital sex so that this could become less risky and more common. There have been some major drawbacks of this change, the principle one being the loss of family stability with many spouses being left to look after children alone. While there has been increased options for women to pursue other roles, and increasing acceptance of single parents or homosexual couples, and the ability to sever some very unhappy marriages, the high divorce rate is not a gain. Humanity may continue to change its social structure, and develop ideas which are universally seen as good, such as lack or race or sexual discrimination, but not all the changes are for the good.

The new reproductive technologies can alter family structure, but compared to what we have already done, they should not be seen as so major. Even the increased life expectancy must have a major effect. The genetic and social parents may be separated, but they have previously been separated when children were adopted, which has occured for millenia, since the practise of leaving babies on the doorsteps of houses or in the market square of Greek towns. Children could also be bought as slaves, for a long period. What is more distinct is that new technologies plan for the births of new children, whereas these examples consider looking after an existing child. However, we then have only to look at the Bible to see a few examples of slaves having children for their masters who were infertile. The idea of surrogacy has a longer history than the hightened concern of recent interest. There have been 500 births from commercial surrogacy arrangements in the USA in the last decade, and despite its legal rejection in Britain and some other countries, it is still accepted in many US states. The new technology has made it more sophisticated, and perhaps more ethical as it does not involve "adultery" itself, but the wider issue has been faced in the past. Rich women have had the chance of letting their slaves bear children for them in the past, though they are not their genetic children. The idea of genetic relationship seems to be very important to our thinking in 1990, given the success of adoption in recent decades, this idea should be weakening.

In conclusion, under some situations I would support the use of AID or embryo donation, they lead to a positive affirmation of the family. They should be used only when the physicians are sure that the child will have a loving environment in which to grow. There should be no commercial sale of gametes. The children should be told of their origin, but whether they should be given the identity of the donor, is a very difficult question. I think that children have some right to know their genetic parents if they want, but that we should encourage the priority of social parenthood over other contributions. I do not support the use of surrogacy in general, but in exceptional circumstances there may be reasons to consider it, as when the surrogate mother is related or a friend of the couple, and if the situation is judged that it will not lead to any future conflicts over the child (it should have no commercial operation).

12. Selective Human Breeding

Natural Genetic Selection

Every human being has a different set of genes, or genotype. The basics of this have been discussed in previous chapters. Sexual reproduction is a risky business, with a relatively high occurrence of mistakes. About 3% of humans born have some genetic diseases. There are at least 4,300 different genetic diseases known that are thought to be the result of single gene mutations (McKusick 1990). In 10% of these the protein abnormality has been defined. There are numerous other multiple gene disorders, and much is still unknown regarding the association between genes and health or disease.

The first steps in the prevention of genetic disorders occurs naturally. Many abnormal sperm cells are produced but only a minute fraction get physically close to the egg. A large number of oocytes that are extracted for IVF are not able to be fertilised, and it has been found that over a third of these have observable chromosome abnormalities (Pieters et al. 1989). Only 40% of conceptions begin to implant in the wall of the uterus (several days after fertilisation). Out of the embryos that are implanted 30% are spontaneously aborted before the mother would be diagnosed as clinically pregnant, and at least 25% are naturally discarded subsequent to the mother being diagnosed as pregnant (Austin & Short 1985). The number of spontaneous abortions from all human conceptions is estimated to be between 45% (Steer et al. 1989) and 80% (Leridon 1977). A large percentage of all conceptions have a chromosomal abnormality (Connor & Ferguson-Smith 1984). About 30 to 40% of human preembryos resulting from IVF are chromosomally abnormal (Braude & Johnson 1989). The magnitude of human pregnancy loss is greater than that of other mammals. During the human life history there are changes in the types of genes that are expressed. If a genetic defect is present in a gene required during fetal life then the fetus may die and be spontaneously aborted. The majority of genetic defects seen at birth may then only be in genes that are needed after fetal life, and were not needed during embryonic growth.

There is a difference in the way that human beings respond to chemical mutagens at different stages of development. Before implantation the embryo is very sensitive, to temperature or chemical agents, and has a very low resistance, and often will fail to implant. Embryos after implantation vary in their response and develop different types of malformation (Zusman & Ornoy 1990). Mammalian embryos have been shown to be much more sensitive to external influences than avian or reptilian embryos. Human embryos are most sensitive to chemicals during the first 8 weeks of development.

Our genetic information is very important in determining our physical character, and some of our intellectual capacity. This is especially clear in cases of

people suffering from genetic disease. The effect that those people have on a family can be good or bad, some people can cope with it and some can not. Some of the suffering that such people have is the suffering that healthy people have in their own minds, as the handicapped people may not know life to be any different to what they have, that is we can impose our life goals into their lives; however, some suffering can be real, especially when they suffer much pain all their life. The suffering of the family can also be very real, and preoccupying.

The word eugenics was coined by Sir Francis Galton, and is derived from the Greek word "eugenes" which means "well born" or "hereditarily endowed with noble qualities". This idea may be separate from the very common view that the mating of people of "good views" is desirable, to give us more offspring of that view, but we will see that eugenic proponents have often retained this idea. This chapter seeks to analyse some of the ideas and themes associated with the long history of eugenic thinking, before examining the question of genetic screening in the next chapter. Eugenics differs from other human activities in that it is an activity in which we are trying to change ourselves, not the environment or other creatures, and therefore is particularly challenging.

Eugenics in Antiquity

For millenia people have had ideas of selective breeding to increase the representation of people with "good genes". Plato had considered the desirability of achieving these ends by subtle, or direct, incentives to control marriage, and/or mating, of supposedly 'fit' human beings. This is what we could call positive eugenics, as opposed to negative eugenics which refers to the policies intended to reduce the occurrence of genetically determined disease. It may be difficult to draw the line between the two with some recent genetic techniques.

Babies born with major deformities were often killed at birth, and sometimes an image in their likeness was made as a type of idol. The most ancient sculptures of double-headed twins are from 6500 BC (Warfary 1971), and many others around the world have been found. The birth of these children was seen in the ancient world as a sign from god, specific predictions were made from each deformity. Consanguineous marriages were banned in most nations of antiquity. In general, the safeguards against degeneration of the human race were isolated, never religiously motivated and seldom were enforced by legal enactment (Jakobovits 1975). The practice of killing off deformed infants was very common until the last few centuries. Martin Luther is recorded as saying that Siamese twins are monsters and do not possess a human soul.

In Graeco-Roman antiquity most families were small, due to disasters like wars, epidemics and famines, and certain practises such as homosexuality, extra-marital relations and celibacy, and a high infant mortality. Methods used to limit the number of offspring included exposure of newborns, some abortion, but little contraception (Eyben 1981). Abortion was practised by Assyrians, Babylonians and Egyptians, but probably not the Jews. Abortion was hazardous to the mother, so exposure was more often used, and was widespread especially among the poor. Sometimes the child was killed by drowning or strangulation, or just exposure in the town market place. Malformed babies were routinely killed as they were considered

a burden on society.

The Spartans used exposure to the environment to kill imperfect babies (Plutarch II). Every father had to present his child to a council of elders. If it was not healthy it had to be exposed, as it would not become a good citizen or soldier. On, the otherhand, if a man had three sons he was relieved from military obligations, and if he had four sons, exempt of taxation. Plato in the *Republic* (Plato IV) advocated the abolishing of private homes and families for a single class of Guardians. The Guardians could then breed and rear children of the highest type using the methods used for breeding animals. Sexual intercourse was to be strictly controlled. There should be "as many unions of the best of both sexes, and as few of the inferior, as possible, and only the offspring of the better unions should be kept as guardians." In *Timaeus* (Plato I) he advocates only the children of the good should be educated. In the *Republic* he recommended that defective babies should be hidden away in a dark and secret place, though it is vague whether he means infanticide, or relegation to the lowest class. Plato was interested in the quality of babies from a point of the State, as have most recent proponents of eugenics. Plato advocated the deceit of citizens in the manipulation of the quality of stock of the human "herd", as he knew people who were prevented from breeding would not be so happy. He would do this by rigging the drawing of lots.

Aristotle also postulates a hierarchy of human worth, men with fully developed virtue(s) being most fully human. Aristotle supported the exposure of handicapped infants (Aristotle IV), though some ancient writers opposed this (Amundsen 1987). The early Roman empire showed increasing respect for human life with the rise of Christianity, though the fetus was not considered so highly as it is today. Abortion became illegal, and infanticide became a capital offence in 374 AD, and after much earlier public opposition. Infanticide of handicapped newborns was practised in more modern times in Europe, especially by the Vikings, and in Japan until this century, and still indirectly in many countries today in cases of severe handicap.

Polygamy is a human behaviour pattern that has affected the genetic composition of human populations. This practise generates a more intense selection between males of that society, as some men are excluded from reproduction, whereas others reproduce more. Sex selection is another long practised method, becoming more common today with decreased family size.

In Jewish law, incest is forbidden, because it is a breach of morality, not because of eugenics. However, it is recommended that a marriage partner should be chosen with the well-being of the progeny in mind, so men should chose a wife prudently (Feldman 1976). Jewish law goes further than others in cultivating the eugenic ideal (Jakobovits 1975). The Talmud rules that a man may not marry into a family of epileptics or lepers, so we could extend this principle to other diseases and it is eugenic. Marriages to insane persons are illegal, and every man has an obligation to chose the partner equipped with the highest intellectual and moral virtues. The verse "cursed be he that lieth with any manner of beast" is applied to those who marry the daughter of a feeble-minded man. Also important is the compulsory dissolution of marriages that are sterile after ten years. There could also be eugenic ideals behind the law which states that if a women loses two husbands by "natural" death, then she can no longer marry, either because of her bad "luck" or "the well of her womb", such as venereal disease. The Jewish approach to eugenics

reveals an awareness of the individual's responsibility to society and the generations ahead (Jakobovits 1975). There is more teaching that the Jews follow that may have eugenic aims: A hidden physical blemish in a bride is grounds for invalidating a marriage. In the Talmud, a Jew is told to be very careful in the choice of a mate (Bava Batra 110a). The faculties that are good for a father to bequeath to his son include 'looks, strength, riches, and length of years' (Eduyot II, 9). The Talmud rules that a man may not marry into a family of epileptics, or lepers, or similar disease. Today that is applied to any serious genetic disease. The Jews of early times did have a knowledge of genetic connections, for example if a son was born, and his two previous brothers, or two maternal cousins had died after circumcision (by hemophilia), he could not be circumcised (Yevamot 64b).

There are various verses in the Bible that deal with questions of reproduction and sexual behaviour. Some of these are clearly for moral reasons, such as "Thou shalt not commit adultery". Others have moral teaching, such as laws against incest, which coincidentally are consistent with eugenic good, that is, less likelihood of genetic disease being caused by combination of two recessive harmful alleles of a gene by forbidding marriages between closely related persons, the reasons for them could be eugenic as well as social (Bassett 1976). Some verses support eugenic ideals, such as the banning of marriage between close relatives (Lev. 18:6-13), and possibly the ban on marriage of people maimed in their privy parts (Deut. 23:1), and the ban on any priest who has a physical defect presenting food offerings to the Lord (Lev. 21:16-23), as they were considered unholy. However, the prophet Isaiah reproved King Hezekiah because he had excused his refusal to marry as a fear that the children would be wicked. The Prophet said "What do you care for the secrets of God? You should perform your duty, the pleasure of God", which is not consistent with advance human planning.

Eugenics in Modern Times

The idea of some groups of human beings being inferior to others was often based on intelligence, or a method prescribed to define this. The rational was called superior to the animal, thus Aristotle claimed women and slaves were inferior by nature because of diminished reason and being closer to an animal state. The 18th century biologists claimed to prove that Negroes' skulls and physiognomy most clearly resembled those of apes thus justifying slavery (Greene 1959). Superiority is often judged by how close people approach to the 'ideal' of intelligence and rationality (Rothschild 1988).

The concept of inherited criminality was initiated in recent times by the Italian, Cesare Lombroso in 1876. This was to be a major motive for the following eugenics programs, the methods of Lombroso were refuted by the English prison doctor Charles Goring but he supported the view that mental deficiency was inherited. Galton(1869, 1883) had written to say genius was inherited, and this was accepted by many scientists, including Darwin (1871). Galton (1883) defined eugenics as the science of improving the "stock". Eugenics was defined by Galton as the study of agencies under social control that may improve or impair the racial qualities of future generations either physically or mentally. He intended eugenics to extend to any technique that might serve to increase the representation of those with "good genes",

in this way accelerating evolution.

A major motivation underneath many eugenicists was also the idea of human progress, that we must be progressing genetically as well as in our knowledge. This was boosted by the theory of evolution, the survival of the fittest was equated with the survival of the best. The best were the best people to cope with modern life. Galton was a cousin of Charles Darwin. Social Darwinists' tended to equate a person's genetic fitness with his social position. Social Darwinist ideology provided a good climate for eugenic thought, and many qualities such as intelligence, temperament and behaviour were believed to be inherited (Ludmerer 1978, Kelves 1985). The eugenicist's concept of the best human was their idea of the "perfect man", which tended to be an intelligent white male of northern European stock, who had been said to have a larger brain. Some eighteenth century philosophers had believed in the possibility of human perfectibility. There was also a fear that the "stock" was deteriorating.

After the publication of Galton's book in 1883, and the growing acceptance of its ideas, he was to inspire and become the Honorary President of the English Eugenics Education Society in 1908. Since then the Eugenics Society, which in 1989 changed its name to the "Galton Institute", has shifted from the early position of defining people like themselves as "more suitable" and various groups of people as "less suitable", to that of supporting the ethical introduction of advances in human genetics. In the first few decades of this century the effort to do this was based on applying the wisdom of animal breeders. An alleged national interest in the quality of the gene pool of the population was valued more than individual reproductive autonomy. The eugenicists believed that they would save the world, and were very optimistic. They varied, as they have in the past and at present, on whether they support merely a programme of incentives or compulsory measure such as state-controlled breeding and compulsory sterilisation.

To present eugenics as a respectable creed many, famous religious leaders, from Christ, down to politicians and artists were sometimes falsely presented as supporters (Searle 1976). Eugenic Societies were created in England, United States, Canada, Scandinavia, Italy, Austria, France, Japan, and South America. Galton left his estate to found a National Eugenics Centre, with the statistician Karl Pearson at its head (Kevles 1985). The Galton Laboratory became the British centre of research, and trained many international scholars. Also in the early 1900's the ideas were well accepted in the United States. The U.S. national headquarters were at the Eugenics Record Office at Cold Spring Harbour, where the leader was the geneticist Charles B. Davenport. Davenport had visited Galton and Pearson at this time. This institute was for the experimental study of evolution. Davenport conducted family pedigree studies over many generations, as he was concerned with Mendelian style inheritance of the genotype, whereas the English were more concerned with the phenotype and often only studied parent and children trends. Whenever family pedigrees showed a high incidence of a given character he concluded the trait must be inheritable, and tried to use single elements of heredity (Davenport 1911). The American Eugenics Society was formed in 1923 combining many smaller committees. The development of eugenics was associated with a political desire to use science to solve social problems (Allen 1989).

A principle concern of the eugenicists was the lower fecundity of family "stocks" from wealthy, and more educated, families. As these people were from

this type of family they had fears of their progeny being swamped by large numbers of progeny from uneducated, and thus genetically unfit, classes. These ideas were around before 1900, but people had been ignorant of the process of heredity. Chromosomes were known to be carriers of the genes only around 1900. This gave a rule for the transmission of traits, so instead of relying on ideas from animal breeders, they now had a biological theory. There was some scientific backing found for Lombroso's and Goring's conclusions on hereditary deficiency, as the idea of the Intelligence Quotient, I.Q., was introduced by the book of Pearson and Jaederholm (1914). This was in the face of many studies showing that traits were determined by complex traits and the effect of the environment, but these were largely ignored.

The eugenics movement was responsible for introducing a social class classification in 1911, with the Registrar General of England, Bernard Mallet, a future president of the Eugenics Society (Austoker 1985). The lower social classes were viewed as the sources of criminals but had greater fecundity. These classes were thought to be caused by genetic, rather than environmental problems, having higher infant mortality because the mothers were incapable. This social class analysis is still used, and has been called an embarrassment to epidemiology.

Public support for eugenics grew. Many churches came to support it, and claimed that the Bible was a eugenic book. Competitions were held to see whose family was the fittest, and displays in fair grounds illustrated the "science" of eugenics. Biology had become popular (Kevles 1985). People also objected to paying many taxes to pay for criminals and for maintaining handicapped people. During World War I intelligence tests based on the Binet-Simon, I.Q. Test, developed by Robert Yorkes, were used to place recruits in their "appropriate" place in the army. After the War these tests were popularly accepted, and Yerkes drew up the standard National Intelligence Test. Courses teaching eugenics were offered in many Universities in the 1920's.

In Soviet Russia in the 1920's there was a strong eugenics movement, centred among the geneticists (Graham 1987). The emigration of nobility, upper class families and scientists, as a result of the Revolution, was seen as a serious loss to the genetic resources of Russia, requiring eugenic correction. In the late 1920's they were criticised, for ignoring the principles of Marxism, which said social conditions determine consciousness. The Bolsheviks advocated a widespread artificial insemination program in the early 1930's, but they lost political power. Herman Muller tried to persuade Stalin that the use of eugenic AID would be desirable, but soon after this the Lysenkoists forced the closure of the Institute of Medical Genetics, and several of his colleagues were shot (Adams 1989). Eventually Lamarckism dominated Russian policy as it was seen as more consistent with Marxism, and eugenics was shunned. The eugenic excesses were used against genetics, to claim it was fascist.

There were eugenic policies in about forty countries, but as can be seen they varied widely in the practises used to effect the idea (Adams et al. 1990). There were sterilisation programs advanced in many countries, as will be discussed in the next section. They were particular prevalent in Northern European countries, such as Scandinavia and Germany, and were rejected in Britain, Holland and some central European countries (Roll-Hansen 1989).

Sterilisation Programs

Sterilisation practises are very ancient, and worldwide. Some early laws such as Jewish law outlaw sterilisation by surgery or drugs. From 1900 to the 1960's the main eugenic practise involved the sterilisation of the undesired. Abortion was officially illegal in this time, and birth control did not reach the poor. Some countries had marriage restriction laws, which were more used in Britain. In Britain less eugenicists were convinced of the necessity of sterilisation than in the USA, and in Britain it was considered by the courts as generally being illegal. The most infamous of these methods were the eugenic practises of the Nazis, but their practises were based on an earlier legal tradition.

In the USA negative eugenics was effected by two major types of legislation: involuntary sterilisation laws and the Immigration Restriction Act of 1924. The first state sterilisation law was enacted in 1907 in Indianna. There had earlier been two unsuccessful attempts at eugenic sterilisation of mentally incompetent patients, in Michigan in 1887 and Pennsylvania in 1895. A publicised turning point was the 1927 court case of Buck v. Bell, where a judge remarked that "Three generations of imbeciles are enough" (Lombardo 1985), and likened sterilisation to vaccination. Analysis of this case revealed that it was probably rigged to provide a model case for eugenic sterilisation. The courts began to invoke the proposition that "common welfare" overrides any "natural right" of procreation. Applied eugenics was more readily accepted in the USA than in England. Laws were also passed in Canada. In 1931, thirty states had enacted compulsory eugenic sterilisation laws, and in 1937, 32 states had such laws. Most of these laws were not rigidly enforced, but by 1935, 20,000 people had been forcefully sterilised, nearly half in California. These laws may be applied to a wide range of "hereditary defectives", including "sexual perverts", "drug fiends", "drunkards", "epileptics", and "diseased and degenerate persons". In the 1930's families who were drawing money from social welfare were encouraged to be sterilised. There was a noticeable increase in the number of sterilisations performed during the Depression, as institution officials were afraid more births of handicapped people would strain social services (Reilly 1987). The situation was changed in a 1942 supreme court case, Skinner versus Oklahoma. The court membership had changed since the earlier decisions, and the Oklahoma law was judged unconstitutional, and marriage and procreative rights of individuals were stressed (Petchesky 1979, Letterie & Fox 1990). In nineteen states these laws are still existing, though under stricter federal control, making it difficult to sterilise mentally disabled persons.

The Immigration Restriction Act was specifically designed to decrease the proportion of poor immigrants from southern and eastern Europe (immigration from Asia had been curtailed earlier) by setting the quotas to the optimum year, 1890 (Ludmerer 1978). Part of the argument was that they thought that these people were inferior, and also that these countries did not enforce eugenic control, so the nation's biological strength would be weakened. In some countries where specific eugenic policies were not accepted, there may still be immigration laws that support such ideals. In Australia immigrants can be excluded if they are carriers of genetic disease (Sillence 1990). Even if countries protect their citizens, they can maintain immigration laws with eugenic overtones.

Some of the conditions thought to be heritable were "nomadism", "shiftlessness", and "thalassophilia" (love of the sea) (Haller 1963). The American

Eugenics program was tied to the European programs. In 1935 the American Eugenics Society produced a major work called "Tomorrow's Children" (Huntington 1935). They estimated several million people were in this category of "feebleminded", epileptics or insane. It recommended that while some of these defects might be "purely environmental in origin", these people would produce defective children if allowed to bring up children. It expanded the number to five million adults and six million children who were"subnormal in education", and another twenty million who failed to finish grammar school (Mehler 1987). It recommended that these people should not be allowed to breed, though not all should be sterilised. Davenport had argued for individual selection, but by the 1920's this had been submerged in a principle of racial- or ethnic-group selection (Kevles 1985). Margaret Sanger, the birth control campaigner, argued that the chief issue of birth control is "more children from the fit and less from the unfit" (Sanger 1923).

The idea of eugenics in Germany was called Racial Hygiene, and was founded by Alfred Plotz in 1895 (Hubbard 1986). He was the founder of the leading German Eugenics journal, and a central figure in the movement from 1900 to 1920's. He did not defend economic competition on grounds of Darwinism, and criticised both capitalism and socialism. He wanted to found a Eugenic Society that would put the good of the future above the comforts of the present. Socialism was too soft on the weak, and capitalism was too hard, but gave too much advantage to the wealthy (Graham 1981). By the middle 1920's there were arguments in terminology, right-wing members prefered "Rassenhygiene", and left-wing members, "Eugenik". People began to criticise the movement saying that science was being subverted to politics, and "race delusion was conquering German science". The left-wing proponents started to use Lamarckism which made them easily attackable from the right-wing Mendelian geneticists. There was also an attack on Rassenhygiene as a bourgeois science serving the ruling class of German capitalists, though they still supported eugenics. The anti-semitism and eugenics programs were supported both by Hitler and some right-wing doctors and eugenics supporters (Kater 1987).

The European laws were modelled and inspired from the American sterilisation laws. The German sterilisation program was based on a law passed in 1933, at a similar time to many other European countries, which were modelled and inspired from the American laws. Earlier, some Germans had criticised the backwardness of German Law compared to the USA in passing eugenic sterilization laws (Lifton 1986). The German law on the "*Prevention of Hereditary Diseases in Future Generations*" played a very important part in the health and population policy, and was subsequently connected with the mass murder of Jews, Slavs and other groups up to the end of the war. The legislation that the Nazis promulgated in July 1933 had been developed in earlier years under the lobbying of Wiemar, and sterilisation had been widely recommended by the end of World War I.

The German sterilisation law went beyond the American laws in that it applied to all persons institutionalised or not, who suffered from disabilities (Kevles 1985). The doctors were called to identify candidates for sterilisation. In America however, some people were brought specifically into institutions so that they could undergo sterilisation, then they were released. The Americans were critical of their government for not implementing the eugenics program as thoroughly as the Nazis.

Though it is unlikely that the Nazi program, that began in 1934 resulted in an increased number of sterilisations being performed in the USA (Reilly 1987). In 1937 the secretary of the American Eugenics Society, Frederick Osborn, remarked that "the German sterilisation program is apparently an excellent one". There was similar ideology and much collaboration between the two programs. There were many Americans supportive of the German laws, some calling them model (Mehler 1987). Ninety percent of the American biology texts from 1914 to 1949 discussed eugenics, many commenting favourably on the German program. The Journal of the American Medical Association frequently published detailed accounts of the Nazi program in a weekly section called "Foreign Letters".

Nazi Eugenics

The goals of the Nazi eugenics program had been outlined in 1933 by Wilhelm Frick (who was executed at Nuremburg). He estimated that 20% of the German population would have progeny that was "undesirable". By 1939, 0.5% of the total population had been sterilised, by 1945 about two million had been sterilised. Most of these people were between 15 and 17 years old (Pfafflin & Gross 1982). In some areas they were more efficient, by 1938 in Hamburg, 3% of the population had been sterilised. It was not until 1972 that these people could apply for financial compensation (limited to 5000 DM). The law was annulled, but remains on the statues, so that orders issued under the law continue to be valid (Pfafflin 1986).

The program involved the establishment of Hereditary Health Courts, with two doctors and one judge. The trials were closed, and no doctor presenting evidence could hold back any information. Medical record offices were established, and by 1938 had every person's history stored. The next stage was to use euthanasia to kill off handicapped people, from 1939. The connecting link to the murders was probably the commencement of the murder of psychiatric patients in the war (Pfafflin 1986). In August 1939 every handicapped newborn baby had to be compulsorily registered (Aly & Roth 1984), where a committee of three consultants would meet to decide the fate. In 1943 the criteria included "gypsy, Jew or half-breed". By 1940 the killing of adult psychiatric patients started, the T4 campaign. Accurate records were kept, up until August 1941, 70,273 psychiatric patients were murdered by gas chambers, this "disinfection" saved 88,543,980 Reichmarks annually on food. After a time the killing was decentralised, and called "random euthanasia", using poisoning or starvation as well. Also part of the reason for decentralisation was loud protests from the church (Proctor 1988). Starvation was used by doctors as a passive means of death if they found active killing too much against their ethical code (Hubbard 1986). Then the 14f13 campaign began to select and eliminate sick concentration camp prisoners, and this led to the "final solution". Euthanasia programs were also carried out in Poland and occupied Russia. Concurrent with this was the "Brandt" campaign used from 1943, against "racial undesirables" and "asocials". The targets were inmates of various nursing homes and juvenile concentration camps. The newborn children of foreign labourers were killed during delivery.

The doctors involved, believed that killing was a medical procedure (Lifton 1986). The doctor had a loyalty to the nation as a "cultivator of the genes", above his responsibility to his patients. The Nazi doctors had a central role in the genocide.

Historically, the main groups of people considered for compulsory sterilisation have been the mentally incompetent, criminals and the poor. People who may not have been able to give informed consent even if their consent was required. There were also the people carrying a genetic disease in the family. In both the American and European literature we see the comparison of removing degenerate human beings from the world with the removing of cancer cells or disease from the body (Huntington 1935). One of the well known doctors of Auschwitz was Joseph Mengele. He became the research assistant of one of the leading figures in eugenics research, Freiherr von Verschuer, where he was involved in twin research and in relations between disease and racial types. In 1943 he was appointed chief physician at Auschwitz where he conducted research on series of families (Lifton 1986).

During the War some English and American Scientists still supported eugenics, and it was said to be of vital importance (Huxley 1941). The idea of euthanasia was also seen in American journals, up to an age limit of 5 years (Kennedy 1942). This idea was accepted favourably by some other American psychiatrists (Hollander 1989).

Sterilisation was not the only method of the Nazi eugenics program. In the interests of improving the German race, biologically sound couples who gave birth could reduce their government loans. There were special subsidies for the third and fourth children born to fitter families. Members of the SS were encouraged to father numerous children with racially preferred women.

The Decline of Eugenics

The eugenic sterilisation programs went into decline in the 1940's, largely because of the eugenic excesses of the Nazis. The Nazi war leaders were executed, including some doctors involved in eugenic practises. Although in its initiation the Nazi program was aimed at the "feebleminded", it eventually led to the systematic extermination of many people, including those who were to be sterilised, and homosexuals, Jews, Slavics, and opponents of the Nazi political views. The Nazi program had failed to separate science from politics (Roll-Hansen 1989). The American and other European Eugenicists' had to be on the defensive, and claimed that these Nazi excesses were the casualties of war. This association of eugenics with racism has been very harmful for its public image, but racism featured in eugenic programs of other countries also. However, sterilisation operations were still performed after the war for another decade, particularly in Georgia and North Carolina in the USA (Reilly 1987).

The Catholic Church had long opposed eugenics, as in Church doctrine, in the scheme of God's creation man's bodily attributes are secondary to the Spirit. Eugenics was condemned by Pope Pius XI in 1930 (Pope Pius XI 1930). Secular critics shared the dislike of biological reductionism, some did not like the growing authority of science, and its intrusion into individual breeding rights (Kevles 1985).

There had been many scientific arguments against sterilisation being an effective measure, and eugenic principles themselves. In 1904 a British Committee appointed to look into physical degeneration, i.e. increasing crime rate, found that the claim of eugenicists was false: the number of criminals was dropping. By the 1920's, many people held that there was no intellectual deterioration either. There was criticism of I.Q. testing, and the growing association of mental deficiency to environmental conditions. There had been work disproving the eugenic stereotypes

of races, such as the American Negros (Klineberg 1935), and by the end of the war public opinion had already switched to believing that there were little innate differences (Kevles 1985). In 1950 UNESCO issued a statement on race, with commentators including the major figures in the eugenics movement, Klineberg, Muller and Huxley (UNESCO 1950). There was a growing emphasis on the importance of the environment in determining the phenotype, with less dependence on heredity (Freeden 1979).

A major proof against sterilisation being effective eugenically was the Hardy-Weinberg Law, from 1908. They had observed that while "undesirable" genes are seen in the sufferers of some diseases, the genes that might be responsible for the traits were widely dispersed in people who do not manifest these diseases or traits. This analysis describes the behaviour of recessive harmful alleles. It was subsequently found that some of these harmful traits have been positively selected in some populations, because in the heterozygous state they confer an advantage on the carriers, for example sickle cell disease in many Africans, and the gene for Tay Sach's disease in many eastern European Jews. This argument is also a powerful argument against future eugenic selection: we do not know the future diseases in which some apparent defect may be advantageous. If we used a sterilisation program against a recessive allele that is in the population at a frequency of 5%, it would take 200 generations of total sterilisation of the homozygous individuals to reduce the frequency to 2.5% of the individuals carrying the allele. Though there would be significant reductions in the number of homozygous individuals born during the first few generations. The presence of carriers who did not express the defective trait meant there would always be potentially new homozygous individuals in the population, and continued screening would be required to detect them.

Some claim that because we are keeping many genetically handicapped people alive long enough for them to reproduce this has led to genetic decay. This has been an argument of eugenics' supporters for the last century (Huxley 1963). This has been a much used argument in the past, but it is not substantiated by evidence. There is no evidence to say that the human gene pool is deteriorating because we can treat genetic disease. Even if there are many people reproducing with the genetic diseases the impact on the gene pool is very slow. In the case of a single recessive gene in the population at a frequency of 0.5%, it might take 70 generations for the incidence of the gene to double, to 1% (Crow 1968). What may be more important is the rate of new mutations occuring, because of environmental hazards such as radiation or chemicals, and the best strategy is to eliminate these hazards from the environment. Certainly prenatal screening and selective abortion can reduce the number of individuals born with genetic diseases. However, the ethical justification for using these techniques is not to be found in protecting the interests of society but on protecting the interests of individuals and their families. This screening can have a major affect on the next generation, for instance the annual number of children born with Tay-Sach's disease in the USA used to be 50, but since the use of genetic screening the number has fallen to 10-12. For the forty families that do not have a child born, it makes a major difference.

A recent study of the incidence of genetic disease in Europe has shown that the incidence of genetic disease among people born is actually falling (Modell & Kuliev 1989). The assumption that medical care to prolong life has led to more handicapped people in the population has been found to be only a minor part of the

influences upon the population structure. People also may think there are more handicapped alive because with modern help they are able to leave the confines of hospitals and houses and enter the wider world. The social and demographic factors are more powerful influences on the frequency of people born with genetic disease. For example the patients can live in open society and are encouraged to enjoy normal life as much as possible, including reproduction. In European countries prenatal screening is offered, which has decreased the incidence of Down's syndrome by 30-60% depending on the country. Improved health care has eliminated heterozygote advantage in malarial zones for some hemoglobinpathies, and the theoretical birth incidence of thalassemia in Cyprus has fallen 11% in the last fifteen years (due to prenatal screening and selective abortion the incidence has greatly reduced). The reduced paternal age has had a consequence of reducing the spontaneous mutation rate significantly also. Population mixing reduces the incidence of harmful recessive alleles in particular localities further reducing the incidence of genetic disease. The incidence of consanguineous marriages is also decreasing. It appears that the aims of eugenicists may be being accomplished but not with their methods which violate individual autonomy but through social changes, together with some influence from genetic counseling.

There has been recognition of the greater importance of nongenetic factors in determining intelligence, criminality and social desirability. It has been found that the trend in the USA for family size to be decreasing can be correlated with an increased level of educational attainment. The less siblings there are, the higher chance of continuing education. Parental interaction may also improve verbal ability, which aids education. However, there are many negative social influences, such as increased numbers of divorces and soloparent families, which has been associated with social and developmental problems.

Changing the Dominance of the Genes

At the time, when we are expecting to soon determine the entire human genome sequence, and when we already have several hundred examples of genes that link to physical and mental characteristics, we also face the older question of how we regard children who are not genetically related to one or both of their parents. The flood of information may have a good effect in diminishing the power of deterministic thinking. Determinism says that because we have a particular gene or combination of genes, we are likely to grow up to behave in the corresponding way. It is the long standing nature/nurture debate. Most accept that we need a balance of views. There are certainly some complex genetic influences upon behavioural variability, the question has narrowed to tracing out the details, and of the mechanisms of these influences.

Recent studies have shown that both nature and nurture are important. In a French study, the average I.Q. of adoptees was higher when reared by parents with a high rather than a low socio-economic status. There I.Q. was also higher if their genetic parents were of higher socio-economic status (Capron & Duyme 1989). This data is consistent with data from twin studies and other adoption studies (McGue 1989). If we want to improve the intelligence and general upbringing of children we should also spend resources to find out what environmental factors are the best for children and then try to improve them. This type of study requires less finance than an approach based on the discovery of all the genetic elements, and

might have a greater positive impact.

The American Eugenics Society changed its name to the Society for the Study of Social Biology in 1972. The social environment was thought by some, such as Muller, Huxley and Osborn to be one of the main directors of natural selection, and that eugenic goals could not be readily achieved in capitalist societies (Bajema 1976, Freeden 1979). Capitalist society is dysgenic (Huxley 1936). Osborn (1940) advocated a type of social welfare state to aid eugenics. The issues of eugenics and the ways it may be implemented in public policy are not just based on genetic ideas, but consider the economic and social system.

Within the next century we should expect to know the answer some of the detailed questions of each trait, as the entire variety of human genes begins to be characterised and categorised and studies extended to tracing the pathways between environmental affects on our genes. It is possible we will become very deterministic in our attitude to behaviour. While our society has strived for greater knowledge, something which is supported by Biblical religions, the ability to decipher the genes of humans ourselves is a pinnacle. Also, associated with this knowledge will be the ability to exert large power and influence. However, we can not run away from the research, there will still be many mysteries of life, and there is enough variety among human beings to ensure that. We must acknowledge the threat of deterministic thinking and move to stress the environmental influences that affect children's personality development.

Control of Reproduction

There is a movement for doctors to become much more involved in aiding reproduction. There aim is to bring about the birth of children with the greatest possible care. One of the aims of eugenics today is the "application of societal measures at improving physical and mental attributes of future generations" (Eugenics Society 1988). This is not in itself dissimilar from most peoples' attitude. It is held by many that it is in the interests of the state to reduce the incidence of genetic disease (Mason & McCall-Smith 1983)

Because of past abuses there are efforts to protect individuals. To counter fears of eugenics the Council of Europe requested "explicit recognition in the European Human Rights Convention of the right to a genetic inheritance which has not been interfered with, except in accordance with certain principles which are recognised as being fully compatible with respect for human rights". Courts have at the same time recognised a "right" for parents to decide whether a handicapped newborn should undergo treatment, or be left to die, in cases such as the Arthur trial in Britain, or the Baby Doe trial in the USA.

Some people had dissociated themselves with the mainline eugenics movements in the 1930's, such as Herman Muller, because they thought eugenics had been perverted into a pseudoscientific facade for advocates of race and class prejudice (Muller 1935). Muller hoped that the principles of evolution would be applied to human betterment, but did not allow his name to be used with any eugenic organisation because of that belief (Carlson 1981). His book *Out of the Night* was written from a socialist perspective. He concentrated his efforts on voluntary positive eugenics, founding a term "Germinal Choice".

There are still arguments for eugenics from economics (Thompson 1979). Some argue that it is a huge cost for society to look after and medically treat handicapped people. About half the hospital beds in USA are said to be occupied by patients whose incapacities have a genetic origin (Smith 1984). The costs of genetic screening are often compared to the costs of medical support (Chapple et al. 1987). As the number of screenable diseases increases as more probes are made then the economics will be even more favourable for establishing genetic counseling clinics. They will need to be run with proper counseling, which increases costs but in the long run is cheaper than dealing with the social problems of guilt and anxiety. These cost analyses are important at times when health budgets are being stretched (Wexler 1980, Evans & Chapple 1988), but we must be careful that they do not become the first criteria that genetic services are assessed by (Clarke 1990).

There is a fundamental question of how far to develop alternative therapies, which are often expensive, versus genetic screening. However, some of the conditions that arise in accidents are similar to the affects of genetic diseases, so technology overlaps so they could be used. There are strong arguments to treat those whose parents do not use genetic screening, but limits on available therapy might be placed. There may be less research spent on some avoidable diseases, but in most cases the same research that discovers the genes that allow screening, also opens the door for research into therapy. We should seek justice in a fair distribution, worldwide, of the health budget. One of the important areas of birth control that is still not distributed very well is access to contraceptives, though in many countries these are becoming easily obtainable. The fears of eugenicists that birth control would lead to a crisis with not enough children have been shown to be misplaced. Some hospitals will insist that if an abortion is carried out the woman must agree to be sterilised, especially in the USA (Mandy 1967). In Britain, the Lane Committee (1974) was set up to look at this practice and called it unethical. It has generally been judged unethical, sterilisation should be performed with free and informed consent only.

However, it would seem to be unethical for the state to refuse to contribute to the care of children who suffer from genetic disease because their parents refused to use genetic screening, as it is unjust to blame the children for their parents actions. It is unlikely that democratic societies would impose selective abortion. In cases of therapy after prenatal screening it is possible, but abortion itself remains controversial. There are economic reasons to favour it, but it still should remain voluntary, at least in countries with private medical insurance. There will be more problems when the time arrives when insurance companies include as a criteria for consideration, prenatal screening. If free choice is lost there will be a large cost in human dignity, the main lesson of the enforced eugenic programs as in the USA or Nazi Germany.

Defects will always be measured against what is considered normal. To be deaf or lame is a handicap for a human being, but they are just as much a person as others. The right to live is based on being a person, and those people still have an equal right to live. This raises the question of what constitutes a human person, and if genetic engineering could be used to change us substantially (Engelhardt 1984). There has been a growing debate on human personhood as discussed in chapter 5. The questions asked include when a person begins, or when a human being begins. Ultimately, they are unanswerable questions, partly because different people will

always mean different questions, so the right to chose up to a point by which it is clear that personhood or a sense of being or self-awareness, should remain. Beyond that point, the fetus must be protected, though it does not mean that we disregard other factors. The point for our current discussion is that a just government cannot enforce a policy discriminating against persons because of handicap, and thus cannot force women to have abortions of handicapped fetuses. The danger of discrimination against the handicapped as a result of selective abortion will remain one that we must be careful to monitor, and some still are against genetic selection for that reason (Beck 1990). We should not forget the eugenic euthanasia of mentally handicapped people in Germany, and how easy it was for their society to accept that practise.

All genetic screening services should be used in a voluntary way. Prenatal tests must be performed on fully informed women with their informed choice. It is desirable for the spouse to be involved, but it should not be a precondition. Neither should it be a precondition to inform the parents of pregnant teenagers, as in several US states. In newborn screening for diseases that can be treated, for example PKU, the practise followed is normally presumed consent, so that unless the parents object, the screening will be conducted. It could be argued that if a relatively common serious condition is treatable the prenatal screening should be performed despite objections of the parents because it is in the best interests of the child.

Carrier screening for recessive disorders is only important for those people who may have a child. It can be carried out when a child or an adult, each point in life entails different problems. Assuming their is no therapy available, priority should be given to people of child bearing age. Carrier testing for dominant disorders has more ethical concerns, and is discussed in the next chapter. There are some mass screening programs for common health problems, they also have ethical problems, and are discussed in next chapter.

In Singapore, the idea of selective breeding is being adventurously tried, by offering incentives to people who are thought to be desirable to have children (Chan 1987). We can imagine the types of advertising campaigns that could be extrapolated to other countries (Etzioni 1983). The Singapore authorities support a 80% hereditary/ 20% environmental influence on a person's intellectual ability, and most often cite H.J. Eysenck. He does not actually claim 80% of the factors determining variance on the I.Q. of a population are genetic (Eysenck & Kamin 1981). In 1984 Singapore implemented two new policies, a "Graduate Mums Scheme" to increase fertility among married educated women, and a sterilisation scheme to decrease the fertility among the uneducated by offering US$ 10,000. There was very strong opposition to the first scheme, and a low response to the second. Chan (1987) has attributed these ideas to "ideological expression of privileged class interest". There were also measures to encourage some individuals not to reproduce, in the form of "anti-poverty measures". The standards used by some eugenic selectors remain falsely optimistic, as even if you select for some positive attributes, every individual has some harmful recessive genes.

Sterilisation of the Mentally Incompetent

The sterilisation of the mentally incompetent is still an important issue. Compulsory sterilisation is performed very rarely in Britain. The Royal College of Psychiatrists considers that sterilisation (tubal tie and vasectomy) should be available

as a method of contraception to mentally handicapped people of all ability levels, as in the general population. Mildly mentally handicapped people may be able to give valid consent. Severely mentally handicapped people who can not give consent may still be sterilised if they are sexually active; there is a risk of pregnancy; and there is sound evidence that they would be incapable of coping with the emotional and physical stress of pregnancy, or of functioning as a satisfactory parent even with a reasonable level of support; and sterilisation is on medical and social grounds the most appropriate form of contraception. However, until 1989 it still required specific court orders to permit sterilisation in these types of circumstances. The House of Lords declared in mid 1989 that in some cases doctors can sterilise mentally-incapable women if it is in their best interests, without the need for High Court approval. In Britain the proposal to sterilise a person for "eugenic" reasons is made after considering the person's individual characteristics and circumstances, the reason is to protect the women from pregnancy and child which they would be unable to look after. If it is for individual cases then it is acceptable. This is unlike some countries where the proposal is based on the individual's membership of specific categories of persons (Kingdom 1985).

Sterilisation in Germany is considered lawful only if voluntary informed consent is given (Eser 1985). There have been several cases in Australian courts supporting sterilisation, for similar reasons to the U.K. criteria, in accord with the basic principle of medical ethics, to benefit individual patients. In Japan the 1948 Eugenic Protection Act was designed as a method of permitting sterilisation, including that of mentally incompetent patients to be performed. Sterilisation is not generally performed for reasons of birth control. The total annual number of sterilisations is low, and has been reducing, to a 1987 official figure of 7,347 of which 7,216 were women (this may only be half the total). Most are performed for reasons of a decline in the mother's health, or risk to her life. Less than 40 are actually listed as genetic or mental disease related. In the case of incompetent persons, the decision is made by the guardian of the patient, but it is still possible for the controlling committee to enforce sterilisation in the absence of substituted consent by the guardian, and in 1987 there were five cases out of the total that this occured. The problem with analysis of any figures is the actual standards used for obtaining consent may vary greatly between countries, as may the reasons stated.

Voluntary sterilisation as a form of birth control is encouraged as part of federally financed family planning programs in the USA (Petchesky 1979), but it is not compulsory, and is not publicly associated with eugenic ideas. Compulsory sterilisation is still performed in the USA (Thompson et al. 1978, Letterie & Fox 1990). As a reaction against eugenic sterilisation abuses, there was a period where courts rejected the sterilisation of mentally incompetent patients. However, during the last decade there have been some cases of courts approving sterilisation. The sterilisation usually requires substituted consent, such as by a parent of an incompetent patient. Such sterilisations are conducted in most states. In the USA there are people who want more choice for the parents of mentally handicapped children (Scott 1986). There are still court-ordered sterilisations performed, and these are said to be justified not because of the perceived harm to society by the presumed inability of the handicapped to serve as parents, but rather for the benefit of the individual concerned. From a consideration of medical ethics practised in most countries today this is the only acceptable criteria, and should be maintained.

There are individual persons, who are unable to give valid consent, but who would reasonably be thought to benefit from the operation. It is distinct from the sterilisation of a general class of person that occured in the first half of this century.

Genetic Disease is not Evenly Spread

Many genetic diseases are distributed unevenly among different racial or ethnic groups. This is because, until this century, breeding was often confined within particular local groups, which resulted in particular mutations being concentrated into particular areas. Some examples of this are represented in Table 12-1. It is important that when a particular test becomes available for screening for one of these diseases in a high risk group, the screening is not perceived as being racially eugenic, like the Nazi eugenics program, or immigration policies that have been (and still are) imposed in some countries.

Ashkenazi Jews have been found to have increased frequency of Tay-Sach's disease, Stub thumbs, Factor XI deficiency, Gaucher's disease and many other lower frequency genetic diseases. Mediterranean peoples (Italian, Greeks, Sephardic Jews) have increased frequency of beta-thalassemia. French Canadians have more Tyrosinemia; Blacks more hemoglobinpathies and glucose-6-phosphate dehydrogenase deficiency. Japanese have more Acatalasia and Oguchi disease, Chinese more alpha-thalassemia; and the list goes on for other racial, ethnic and religious groups. This means that many screening efforts, due to shortage of resources, will be limited to these high risk groups.

Table 12-1: Genetic Disease Frequencies in Specific Groups. The conditions listed are found predominantly in the groups listed in the Prevalence column (adapted from OTA 1984).

Condition	Prevalence
Cystic fibrosis	1:1,600 Caucasians Live Births
Diabetes mellitus, type 2	1:130 Caucasians
Gaucher's Disease	1:2,000 U.S. Jews
Glucose-6-phosphate dehydrogenase deficiency (A-type)	1:11 U.S. Blacks (male)
Intestinal Lactase Deficiency	1:10 Caucasians (also in other races)
Occulocutaneous albinism (tyrosinase - type)	1:39,000 Caucasians 1:28,000 Blacks
Occulocutaneous albinism (tyrosinase + type)	1:37,000 Caucasians 1:15,000 Blacks 1:150 in certain American Indians
Primary gout: idiopathic	1:500 Western Populations 1:50 in American Males by 50 1:10 in males in some Polynesians 1:25 in females in some Polynesians
Sickle Cell Anemia	1:500 U.S. Black Live Births
Tay-Sach's Disease	1:3,000 U.S. Jews

Common Themes

There have been some common themes throughout the history of eugenics that this brief survey has covered. Some of these explain why eugenics has been, and is, a potentially dangerous activity. We can apply these ideas to modern practice, and may learn from mistakes in past thinking, and from the adverse implications, both direct and indirect, of eugenic policies.

The individual's right to free choice in marriage has sometimes been prevented. There are some cultures which encourage children to seek genetically fit spouses, such as Jewish teaching, or broader social policies based on family approval of marriages, such as in India or Japan. Other cultures may less positively pursue the same choices, and it is impossible to prevent some discrimination. Some societies in Middle Eastern countries may promote more consanguineous marriages which have the opposite effect, a higher incidence of genetic disease. What we can avoid is for a society or governmental social policy to condone eugenic selection. There is voluntary premarital testing in some communities, which is ethical if used as such. To avoid potential stigmatisation, the results should be only disclosed to those directly involved or kept confidential via an intermeditory.

The individual's right to reproduce has been prevented, by compulsory sterilisation measures. As society has opposed these compulsory measures, there has been a growing move to voluntary measures, though these measured may be more enforced by peer group pressure to conform and by financial costs if the State does not provide medical care. If health care becomes centred on private medical insurance companies, there could be more pressure not to bring disabled children into the world, as the insurance companies could insist on prenatal screening.

The major use of eugenic selection occured together with the move to a more scientific worldview. This is because of both the development of scientific techniques, from sterilisation operations, AID, genetic screening to gene therapy in the immediate future; and from the associated cultural values. As our genetic knowledge greatly increases we must note this tendency. We must be careful about the possible growth in genetic reductionism that could come from the detailed analysis of the human genome. This will be a challenge to existing human society, and will need to be introduced slowly, in a way that is sensitive to any adverse social consequences.

Eugenic measures often end up with racial or social group overtones, more then breeding from the "best genes". The model chosen depends on the society, for instance Spartans wanted good soldiers, geneticists from the middle-class want well-behaved middle-class, and the Nazis wanted blonde, blue-eyed, Aryans. We must have a clear view of human dignity founded in individuals possessing equal value not dependent on their ability or performance of some task.

For all of history people have prefered to have their children born free of genetic disease. With modern medicine many handicapped people lived much longer, to avoid the need to have these people born, genetic screening is developing. The actual number of people born with genetic disease has not substantially increased, and may actually be falling. The criteria of selection of "disease" will vary with people, but with a general move from "taking what is born" to selecting the type of baby we do not want to be born, eventually to selection of the children of qualities that we want. There will be less severely handicapped newborns if selective abortion is increasingly used, and eugenicists will have new methods. The name has

also changed, from eugenics to genetic counseling; we must ensure the focus has also changed, from not just societies interests but to protecting individuals.

The concern's of society are often placed above the rights of individual's when eugenics is developed, and this is the fear held by many today. Eugenic measures have been used in societies under different circumstances, and eugenicists have included both sides of political opinion. We must be aware of our modern medical practise in the light of eugenics and the associated attitudes (Neuhaus 1990). The opposition to eugenics may come from the concern for the rights of individuals, both those born, and fetuses; belief that we should not interfere very much with nature or God's purposes or chance; or that it conflicts with some political view, such as the earlier Russian Marxist view that all humans are given equal ability. The Christian opposition is based more on the view that all humans are given equal status or rights, which is not the same as ability.

This is not just to say that the new eugenics is all bad, in fact most people support some genetic counseling, including myself, and many of a variety of philosophical and religious views. The lesson from history may be that we must be very careful where we draw the line, and that it remains voluntary. There are some important areas of reproductive choice which should be left up to the individual or couples.

The Quality of Life

The quality of life needs to be considered, we should work for developments to improve the biological, social and spiritual quality of life. One of the first questions a mother asks after she has given birth to a child is "Is my baby all right?". It is more important than the sex of the child, about 1 in 30 children have some genetic abnormality requiring medical attention (Seller 1982). Most of the genetically abnormal individuals are spontaneously aborted in early stages of pregnancy. Human procreation is associated with a high degree of error, because when genetic elements rearrange there are often mistakes (Bodmer & Cavalli-Sforva 1976), but most affected individuals die before birth.

The spontaneous abortion rate is higher in older women than in younger women, probably due to the larger number of genetic abnormalities. In one sample of women scheduled for chorionic villi sampling at 12-14 weeks of pregnancy, the times at which spontaneous abortions were observed was measured (Cohen-Overbeek et al. 1990). The rate of spontaneous abortions within thirty days after the program intake time of between 6-10 weeks was 2% in women of age 35-36 years but 11% in women of 40 years age and older. The majority of the aborted fetuses were genetically abnormal. The majority of abortions occured at 10-12 weeks in these women, and the writers suggest that this justifies delaying prenatal testing until the "natural" selection process has occured, by performing tests at 12 weeks of gestation. This illustrates that genetic selection is to some extent a normal part of human reproduction, and what we must consider is how far we can extend this process.

The number of fertilised embryos with genetic abnormalities may be about 70%, a very high figure compared to simpler animals. Often the parents of the children with severe disorders know that the child they are to have has a high chance

of having the disease, either the child will or won't if it is caused by a single gene defect. So those couples can have a child, with the process of genetic screening involved to check that the embryo is not inflicted. If it is inflicted they may choose abortion and then try to have another fetus, knowing that if they have enough attempts one fetus will not suffer from the disease, and they will end up with a healthy child (with respect to the trait that they are screening for). If we accept this as a valid choice, the scientific problem is that antenatal diagnosis does not work until the embryo is 8 or 9 weeks old. This may be considered too late for abortion if we take the status of the embryo to be of protectable state before that, however it can be consistent with the arguments on embryo status considered in chapter 5. It is legal in many countries to have an abortion at that age, and it is probably prior to "brain life". It is possible to diagnosis diseases at a much earlier stage, which will enable abortion at a more "acceptable" age, though while *in vitro* assays are easier than taking samples *in vivo* , successful implantation is still a major hurdle.

Important from a religious perspective is whether we deny the potential for spiritual relationship between God and man in what are the most diseased forms of human life? If a fetus has a serious genetic impairment, with a consequence of serious mental deficiency, some people might say that the fetus does not, and will not in the future, have a "life" as "normal" humans have a life, it's potentiality is different. Still many believe potential spiritual relationships are present in all human fetuses. The quality of man, the soul, his essence, his unique individuality, with its associated dignity or reverence means that man has a sanctity.

In the Christian perspective there are no "worthless" lives, since in God's eyes each human person is precious (Bryant & Bankowski 1985). In the allocation of society's resources these values emphasise equity rather than social merit, social productivity, quality of life, or ability to pay. A related question is euthanasia, or letting people die to avoid life's tribulations. It is different to prolonging life aimlessly by technological means, because there is a time to die for all, for some earlier, and for others later, but active intercession to aid death is against Christian belief.

It is ironic, but important, to remember that a disease that might seem to make someone "less human", in fact may make others around them more human in the love and care that they give. There is a strong idea that ideal ethical behaviour is keeping with our true humanity, we need to be able to love to be "wholly human" (Schuller 1986). Often much of the suffering we see in others is what we would imagine they feel if they had our sense of what is suffering (Hauerwas 1986). The suffering that is being avoided may be more that of the family than the actual individual.

We do not need to maintain life at all costs, as this may not be in the patient's best interests or in God's will. We are not vitalists, we do not preserve vital or metabolic processes with no human feeling or capacity for that. This idea is especially essential with modern technology for sustaining of the vital functions of human life, and is recognised by most people. One of the early statements on the distinction between extraordinary and ordinary treatment came from the Pope Pius XII (1957); "We are normally held to use only ordinary means, according to the circumstances of the situation, but are not obliged to any grave burden for oneself or another to life... Life, death, and all temporal activities are subordinate to spiritual ends." What is considered is the quality of life.

The quality of life relates to the individual person, and conceptions of it change with time and situation. People have different hopes and ambitions, and the capacity for personal growth from a given state is important. The absolute sanctity of life principle has been criticised by many writers (Kuhse 1987), who have shown how we do not practice such a system but rather make decisions regarding the quality life, even if officially some governments (such as the U.S. Government in 1982) have said these decisions should not be made. A crucial point needs to be made, which is often unnoticed, these decisions do not make a judgement on the value of different human beings. Rather, these decisions can be made with regard to the patient's best interests, which is not always the prolonging of life. This distinction has been made in the past, for instance in fighting in a "just war", or the exceptions given above, the decision does not involve a question of the relative value of human life. One definition of untreatable might be the patient is unrestorable to acceptable self-awareness, or reasonable health. In practise an absolute sanctity of life principle does not work, but it is still necessary as a general rule to protect people. One approach would be to take up the terminology of Paul Ramsey which involves dying and nondying patients, and it being possible to sometimes refrain from preventing death.

Often supporters of the sanctity of life principle deny that their judgements consider the quality of life, and speak of distinctions between acts and omissions, causing death and allowing death to occur, ordinary and extraordinary means of treatment, and intending death or merely forseeing that death will occur as a consequence (principle of double effect) (Kuhse 1987). To be consistent it is necessary to maintain a qualified sanctity of life principle. This does not necessitate assigning different values on human life, but can be argued to be in the best eternal interest. Especially so for those who have religious hope of an afterlife, such as Christians, where value is measured in terms of the Kingdom of God, not this world. We must understand our duty to treat and live in terms of man's transcendent destiny.

It is important to identify how life will be experienced by the person to be living in it, as well as how the person's life will be appreciated by others. Many are reluctant to acknowledge that burdens to others should play a role in decisions whether to try to save a patient's life. Lives of individuals cannot be saved at any cost, there are limits to the amount of blood that can be transfused, or the number of kidney transplants, where resources are scarce both in terms of body material and money. There are also emotional and psychological burdens to the patient and to relatives which play some role in a family that makes decisions involving all members.

The distinction between acts and omissions is often not consistent, as in cases of letting severely handicapped newborns die. However, it may be a useful legal barrier as there is the existence of a potential slippery slope to widespread euthanasia. The law has recently been altered in Holland allowing some active euthanasia, the results will be watched in other countries. An objection used by many to this is that it is interference with providence, but in a modern hospital one could argue that many medical treatments interfere with nature, and this is a situation that most are in favour of, as discussed below. If we regard life as sacred, then we may not agree with the modern concept of the right to decide our own life, or autonomy. If we intervene to prolong life with experimental therapy this can be just

as much playing God as shortening may be. The question of euthanasia is not addressed in this book, but some principles are shared to those needed for examining the question of genetically selective abortion. There are changing attitudes in the decisions whether to forego life-sustaining treatment, which is a related issue. In the USA the trend is towards the relaxation of criteria for decisions, and also the incorporation of food and body fluids in the category of life-sustaining therapy in patients in permanent vegetative state (Sprung 1990). It is made easier for patients who may have signed a "Living Will", but in the case of the fetus there is no such letoff. The difficult decision must still be made.

The issue of the value of life is fundamental in many issues in bioethics. This question is important when considering the financial investment into new technology including new genetic technology, offset against the cost of life if using genetic screening and such negative means. Despite ideals of wanting to treat every disease, there are limits.

13. Genetic Screening and Selection

Genetic screening is being applied to plants, animals and man. The subject of this section is medical uses, as there are few direct ethical dilemmas from genetic screening of nonhumans. The technique is widely applicable, and over the next few decades it will be widely applied in agriculture as well as medicine. A feature of good medicine is prognosis, the prediction of the course of disease. Some type of screening may be required before any disease treatment. The physical screening of protein or genetic abnormality may allow detection of a disorder before there are any physical signs of it, or even before a gene is expressed if it acts later in life. Out of the 1500 serious genetic disorders identified, over 200 can be tested for (Fletcher 1988b, Knoppers & Laberge 1990).

Every individual has a unique DNA sequence. There is also much variation between different alleles of each particular gene. Some variations in gene sequences are neutral, and others have positive or negative influence. Genetic screening is the testing of this variation, the same as we may screen people according to their weight. The purpose is to determine whether an individual has the certain test characteristic or not. In terms of molecular genetics the screening may be either of a protein or of a DNA sequence. The screening of a DNA sequence is the most powerful and the type of test that will be increasingly used, though protein testing has often been easier. Usually genetic screening involves the detection of a harmful gene sequence. It is possible to screen for a desired sequence also, as in the detection of the Y-chromosome if sex selection is the goal.

Genetic Screening With DNA Probes

The basic principle relied on is the binding of a probe to the DNA molecule of the patient. Complementary DNA nucleotide sequences bind to each other. The probe used is usually single-stranded DNA , which binds to the test sample. It is applicable to any DNA sequence. DNA probes have many uses for genetic analysis, in all living organisms, but this chapter will focus on human genetic screening. DNA probes have many benefits for parts of medicine that I do not discuss, such as use in epidemiology (Gibbs & Caskey 1989).

DNA probes that are independent of family history are preferred as probes. This means that no prior screening of the parents is necessary. This avoids the need for obtaining consent from other family members for the taking of DNA samples. Prior to this the situation was that DNA samples were taken from parents and other family members. They were usually taken after the birth of the first affected child. These samples can then be analyzed by a technique called restriction fragment polymorphism (RFLP). In this technique the DNA sample is cut up with a mixture (or a particular) of restriction endonucleases, which cut the DNA at specific

Table 13-1: Genetic Diseases that have DNA probes available.

Disorder	Frequency/1000livebirths
Autosomal Dominants	
Hypercholesterolemia	2.0
Polycystic kidney disease	0.8
Huntington's chorea	0.5
Neurofibromatosis	0.4
Myotonic dystrophy	0.2
Polyposis coli	0.1
Autosomal Recessives	
Cystic fibrosis	0.5
Phenylketonuria	0.1
Sickle cell anemia	Race specific (see Table 2-1)
Thalassaemias	Race specific (see Table 2-1)
X-linked Recessive	
Duschenne muscular dystrophy	0.3
Haemophilia (A & B)	0.1

sequences, and then the mixture is size separated, and examined. The pattern of size distribution is quite individual, and the disease causing or linked fragment can be found, and examined in any children or fetus. The results are not always clear, for instance in sickle cell anaemia prenatal diagnosis was only possible in 60% of cases. There are clearly advantages in using family-independent DNA probes. They can be used for all pregnancies without a history of genetic disease. Many genetic diseases arise spontaneously in each generation so would not be predicted. The parents who are carriers of recessive harmful alleles do not need to be screened and marked as carriers, which can have harmful psychological and social problems.

Most progress has been in disorders due to a defect in a single gene. The mutations consist either of single bases changes, affecting a single amino acid in the critical regions of proteins; or else gross abnormalities such as deletions, insertions, or rearrangements of genes (Antonarakis 1989). The number of disorders that are screenable is measured in the hundreds, and is rapidly increasing (OTA 1986). Examples of some single gene diseases for which gene-specific probes are available, though not necessarily for all mutations that cause the disease, are given in Table 13-1. The screening can be performed prenatally or postnatally, and most of the autosomal dominant disorders have a late onset so that clinical signs do not occur until later in life. The problems of Huntington's chorea are discussed later, as they are representative of the dilemmas faced.

One problem is genetic heterogeneity, that is, the disease-causing mutations could occur anywhere in the gene, and there are also many mutations that do not cause disease. It is possible to use different probes to cover many different mutations, but it can never be 100% sure of a negative result for a disease. In some diseases, such as Huntington's chorea, there is no evidence of heterogeneity, however, in bipolar affective disorder, there is heterogeneity. There are at least 46 distinct alleles of the gene phenylalanine hydroxylase (a mutated allele is responsible

for the disease PKU). There are mutations found in each of these alleles, which would make total screening impracticable (Levy 1989). It may still be possible to screen for common mutations of diseases. A single test for one cystic fibrosis mutation would cover 70% of the observed mutations in Caucasians (Ballabio et al. 1990), but numerous other mutations are also observed. It requires experience of each disease to decide how to screen and the probabilities.

For common genetic diseases, screening for predominant mutations may still be a worthwhile goal. Cystic fibrosis affects about 1 in 1600 births among Caucasians. Approximately 70% of the mutations correspond to a specific deletion of 3 basepairs at amino acid position 508. A simple therapy, but it is not necessary to use germ-line therapy as embryo screening should be adequate. However, we will still have people suffering from genetic disease, who should be treated. There will be a place for somatic cell gene therapy, together with other therapies. There may be one for germ-line therapy when it comes to future generations, but that requires much more discussion.

There are also differences in expressivity, one person may express the disease to a different extent, or at a different age, to another. Sometimes this is due to multiple gene activity, or the presence of some environmental factors as is the case with Wilms Tumour, or Retinoblastoma, or Glucose-6-phosphate Dehydrogenase deficiency. The progress and severity of genetic diseases does vary (Holtzman 1988).

There is much commercial interest in screening, as the market is very large. Companies are working on many diseases, and packages that can screen a hundred or more disorders should eventuate in the near future. There is a very large commercial market, though it is much less than the huge pharmaceutical industry. It is best for the patient if only one sample is taken, and as many tests as possible are performed. There is a shortage of trained personal for genetic counseling, and will be for some time, as the new clinics are established. It needs to be done only in clinics with good support for counseling.

The DNA probes and genetic information is perceived to be 100% reliable by many people. Public attitudes need to be educated against this type of blind faith in genetic techniques, that we saw 70 years ago. That is a lesson of the eugenics programs of history. Many tests can be made, access will need to be made fair. The uncertainty of prognosis needs special stressing in multifactorial disorders, and psychiatric diseases.

Another problem is that many genetic diseases occur spontaneously, and are not inherited from the parents. This is true for about a third of the cases of hemophilia and a half of muscular dystrophy. It is also true for the chromosomal aberrations (Chadwick 1987). In retinoblastoma, many cases are new germline mutations, arising in egg or sperm, or the early embryo. It has been found that new mutations for this disease occur more frequently in the paternal chromosome. This could be because new mutations at this gene locus arise more frequently during spermatogenesis than during oogenesis, or that imprinting in the early embryo affects chromosomal susceptibility to mutation (Zhu et al. 1989). As we discover more, we may be able to lower mutation rates.

Postnatal Genetic Screening

There are various applications of genetic screening. The screening of adults to predict their susceptability to disease may be important in certain industrial environments. It can also be used by medical insurance companies. There is also screening with an eye towards reproduction. The screening of people prior to their marriages being allowed occurs in some states of the USA and in Denmark. It may also be used for fetal screening, with the view to selective abortion of genetically diseased fetuses.

The first major type of genetic screening used by medicine was screening of newborn children for PKU deficiency. In the 1960's it was made compulsory in the USA. It is the most widespread screening worldwide. If a newborn is found to have PKU deficiency, they can be put on a special diet, and will not suffer from severe mental retardation that would otherwise result. As well as a very major healing motive, it also works out economically cheaper to treat patients before serious damage is done to them by the genetic disease, than to the costs of keeping the sufferers in institutions.

In several states of the USA there is screening for a haemoglobin disorder, sickle cell disease, and it is compulsory in seven states. Hemoglobinpathogies are a major health problem in the USA, an one treatable part of this condition is the increased susceptability to severe bacterial infection during the first few years of life (NIH 1987). If the children are placed into care programs than they have much better health, which is a key justification for widespread screening. Some of the other disorders currently screened for in newborns are hypothyroidism, galactosemia, homocystinura, and maple syrup urine diseases. There is little debate on whether newborn screening for serious avoidable genetic disease should be voluntary, or compulsory, as we discuss later. It is generally performed presuming consent. New techniques for the amplification of DNA from dried blood spots using the polymerase chain reaction (PCR) can be of use in examining the molecular basis of the positive results. Such tests are possible from dried blood samples, and have been performed for sickle cell disease (Jinks et al. 1989), phenylketonuria (Lyonnet et al. 1988) and cystic fibrosis (Ballabio et al. 1990).

The American Academy of Pediatrics (AAP 1989) has circulated sets of fact sheets which provide information to pediatricians. There is a growing number of tests available, at different costs. Some of these characteristics are presented in Table 13-2. In some of the diseases complete health restoration is possible. The frequency can vary between races in some cases. The costs of testing are given when several are jointly offered, as is common practise in developed countries. The advent of DNA testing will make a broader range of tests available.

Table 13-2: Some genetic diseases that can be tested for in newborns (AAP 1989).

Disease	Health Restoration	Frequency, live births	Testing Method	Cost US$
Biotinidase	Complete	1:70,000	Enzyme assay	0.50
Branched Chain Ketoaciduria (Maple Syrup Disease)	May be Complete	1:250,000	Bacterial Growth Inhibition	0.50
Congenital Adrenal Hyperplasia	Complete	1:13,000 Eskimos 1:680	Enzyme immunoassay	1.50
Congenital Hypothyroidism	Yes	1:4,000	Radioimmunoassay	1.50
Cystic Fibrosis	Yes	1:2,000	Immunoreactive trypsin	1.00
Duschenne Muscular Dystrophy	No	1:4,000 male	Enzyme assay	10
Galactosemia	Complete	1:60,000	Microbiology or Enzymatic	0.50
Homocystinuria	Yes	1:50,000+	Bacterial Inhibition	0.50
Sickle Cell Diseases and thalassemia	Yes	1:400 in US Blacks	Protein electrophoresis	1.50

In Japan, there has also been mass screening for neuroblastoma in three month old infants, utilising the time at which a neonatal examination is normally performed to minimise expense, and to ensure maximum public coverage. There are other diseases that may be added, at this stage, and there is a good case for compulsory screening if there is therapy available. Other diseases will be added as cheap, easy, save, predictable tests become available. Genetic screening has a parallel to vaccination programs that have been compulsorily introduced. Though the vaccination program has public health aims for the prevention of infectious, not genetic disease. Vaccination often has some low risk of harm to individuals.

There is screening for genetic susceptability to suffer from environmentally induced disease, like elevated blood cholesterol, which can advise us to alter our behaviour to lower our risk. This is an extension of preventive medicine. The programs for the detection and treatment of individuals with elevated serum cholesterol levels have been advocated in most developed countries (Pearson et al. 1990). In 1968 the World Health Organisation (WHO 1968) recommended criteria for a condition worthy of a screening program, which are as follows:

1. The condition sought should be an important health problem.
2. The natural history of the condition, including the progression from latent to apparent disease, should be adequately understood.
3. There should be a recognizable latent or early symptomatic stage.
4. There should be an accepted treatment for patients with recognized diseases.
5. There should be an agreed policy on whom to treat as patients.
6. Case finding should be a continuous process and not a once-and-for-all project.
7. A suitable screening test should be available.
8. The test should be acceptable to the population.
9. Facilities for diagnosis and treatment should be available.
10. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on

medical care as a whole.

There are several diseases which could be screened consistently with these principles in developed countries. Other worthwhile mass screening programs include smoking habit, cervical cancer, breast cancer (mammography) and alcohol consumption. There are other possibilities such as hyperlipidaemia, obesity and faecal occult blood (Fowler & Mant 1990). There are still major problems with such programs. Although individual screening is very useful, mass screening is desirable for some. The method of doing this must be voluntary, but if it is left to people to come to a clinic for screening only certain types present themselves. There must be widespread education to inform people of the possibilities. To be effective the programs should allow wide access to the population, and good quality assurance both in the screening and any subsequent treatment. Good public registers are needed. Good ethical and scientific training of the health care professionals are required, as for all screening programs. There is usually a lack of personal to perform adequate follow-up of patients, which becomes even more critical in emotionally upsetting results.

It has been found that many common cancers, including colon, lung and breast cancer, develop by the stepwise accumulation of mutations affecting many genes. The changes include the loss of several "suppressor" genes, which normally inhibit cell growth. Analysis of the gene changes may aid the prediction of how cancer in different patients will develop, and can also be used to warn people that are close to developing cancer. If they already have 7 of the 8 gene changes required to develop cancer, then they should avoid agents that cause gene mutations (such as cigarette smoke). There are some genes that make people susceptible to certain types of cancer, requiring the presence of a mutating agent to develop. It is the accumulation of changes, not the specific order they occur in, that is important for cancer development (Marx 1989b). A particular diet or life style can be suggested to lower risks. There is a link between emphesyma, a lung disease, and a deficiency in a protein called alpha anti-trypsin. When people are screened and found positive, they know that if they smoke, they have high chances of lung disease. Some people may attack this as limiting freedom, however most people would prefer to have the additional knowledge, and another choice if they take heed of it.

The information obtained by population screening can be stored in a registry for later recall before marriage. Premarital testing can be used to exchange genetic information before marriage if people are concerned about possible genetic diseases in future children. If two carriers of the recessive gene for cystic fibrosis are married, then they will have a one in four chance of a child who will suffer from the disease. If they do not want to use selective abortion yet do not want to risk such a child, then premarital screening could be used. It has been used successfully with Tay-Sach's disease as I describe later. Some theologians, such as Paul Ramsey (1970) or Bernard Haring (1975) are in favour of such testing to protect the ignorant and avoid "complicity in tragic birth". Ramsey would approve the use of the United States' marriage-licensing laws to prevent the transmission of very bad genes. While it may be true that no one has an unqualified right to have children, it may not be right to approve of such law enforcement to prevent marriages. In Denmark, marriage licenses are refused to persons carrying certain genetic defects until one has been sterilised (Nelson & Rohricht 1984). This is a dangerous step towards eugenics, and should be resisted. As discussed in the last chapter, it is important to

maintain voluntary use of new techniques, if people are educated most will try to avoid their children having a genetic disease, compulsion by law may turn people away from seeking aid and make them suspicious of the technology in general.

Prenatal Genetic Screening

Prenatal genetic screening has been used for several decades. It has become associated with normal prenatal care in most industrialised countries. There are some important nongenetic screening programmes. For example, if a woman is not immune to rubella, she should be immunised before becoming pregnant. There are other infective hazards to the fetus, such as toxoplasmosis, cytomegalovirus and herpes virus, which are also important for potential mothers to be immune to (Bull 1990). About 80% of pregnant women in France have evidence of past infection with toxoplasmosis, and if they are infected during pregnancy there is a 40% chance that the fetus will be infected. DNA screening services can be provided at low cost (US$3 or less) for some single gene disorders (Beech et al. 1989), and the costs will come down with the greater number of gene probes that are available in easy to be used packages. There have been extensive studies and use of DNA testing during the last few years in some countries, such as the U.K. (Harris et al. 1989, Rona et al. 1989).

Recombinant DNA techniques were first used for prenatal selection of sickle cell disease in 1982. For a growing number of genetic diseases, methods have been developed to detect the genetic defect early in fetal life. These methods rely on removing a sample from the fetal material and analysing it. There are different stages at which fetuses can be screened for genetic disease or abnormalities. As far as the ethics and the distress and the health risk to the mother are concerned, the earlier the better. Types of screening are illustrated in Table 13-3.

Table 13-3: Types of Prenatal Genetic Screening

Type	Time	Risk	Application
Embryo biopsy	2 days	?	Embryo Transfer
CVS	6-10 weeks	1-2%	Wide
Amniocentesis	12-16 wks	1%	Wide
Fetoscopy	14+ wks	3-5%	Wide
Mat. Blood Sampling	2+ weeks	0	Total
Ultrasound	8+ weeks	0?	Total

Fetal sampling is laborious so that currently only a small proportion of the population, can be screened even if it is considered desirable. Hence often samples are taken from those fetuses considered at high risk, i.e. those of older mothers or parents who have a history of genetic disease (Dilella et al. 1986). The older technique used is amniocentesis, where cells from the amniotic fluid are removed and grown in the laboratory for analysis. No harm is done to the fetus as the fetus

is surrounded by discarded cells in the amniotic fluid which are no longer needed for further growth. The fetal samples can be taken at 13-16 weeks. There has been a recent attempt to try to use amniocentesis at 8-14 weeks, but it found 12 weeks was the earliest reliable age for providing sufficient material for analysis (Rooney et al. 1989). It is often performed up to 18 weeks gestation.

It is now possible using very sensitive genetic probes to take a sample of the chorionic villi (membranes around the fetus) at 6-9 weeks and analyse the fetal DNA directly to determine whether it has a specific genetic defect, with the technique of chorionic villi sampling (CVS) (Rhoads et al. 1989). Like amniocentesis there is a 1-2% risk of miscarriage after the sampling due to the procedure. Further developments will bring wider applicability and increased sensitivity allowing earlier detection. We are still unable economically, ethically, or socially, to screen every fetus for so many diseases, with these techniques. They are currently used for screening fetuses from parents of high risk, however, if in the future cheap multiple screening techniques become available it may be possible they will have widespread use.

Fetoscopy involves examination of the fetus by percutaneous transabdominal uterine endoscopy, and anatomical malformations can be directly visualised. In common language this means that the fetus can be viewed through a hollow tube which is inserted into the amniotic sac. It may also be used for the removal of a sample of tissue from the fetus. The recently developed technique for the sampling of fetal blood is called percutaneous umbilical blood sampling. During this technique, an ultrasonographically guided needle is inserted into the umbilical blood vessel to withdraw a sample. The procedure can be performed on an outpatient basis, and does not require maternal sedation, and is safer than fetoscopy. It is still experimental (Hansen & Slavek 1989). Embryonic tissue biopsy is more dangerous, and unknown. With the improvements in genetic screening, it should be unnecessary if genetic diagnosis is desired.

Different methods may be combined, for instance the first screening may be maternal blood sampling, and if certain proteins are detected, CVS or aminocentesis may be used to detect spina bifida, or Down's syndrome. Ultrasound is routinely used, and has the advantage of being noninvasive. In West Germany, all pregnant women have been offered two ultrasound examinations since 1980, one week before 20 weeks gestation and a second at 31-35 weeks gestation. In the U.K., more than 80% of pregnant women undergo an ultrasound, but in the USA only 30-45% are scanned. In developing countries there are insufficient resources to allow routine screening. The optimal time for general screening using ultrasound is currently thought to be at 18 to 20 weeks gestation (Crespigny et al. 1989).

Maternal blood sampling at 14-16 weeks for a protein alpha-fetoprotein is routinely offered in the United Kingdom, and in some states of the USA such as California. A high level of the protein may indicate neural tube defect, and a low level may indicate Down's syndrome. The analysis of maternal blood for the level of alpha-fetoprotein, human chorionic gonadotropin and estriol, can lead to the detection of 60-70% of trisomy-21 (Down's syndrome) pregnancies. This is economically viable for mass screening, but further requirements are desirable, cost-effectiveness is one part of the ethical equation. If the indications are positive for the possibility of a fetal disease, then fetal sampling can be performed, as maternal blood screening is only an easy preliminary screening. A positive result only selects

patients for the fetal screening. In California, all women have to sign a consent or refusal from for this voluntary testing, and can withdraw at any point from the program. Neural tube defects affect about 1 in 500 newborns, so are very common.

Because of the limited resources for genetic counseling services, not all woman, even in developed countries, can obtain services (Emery 1990). The indications that may be used for invasive testing, such as CVS or amniocentesis, include:

* Maternal age greater than 35 years (higher risk of chromosomal disorders).
* Abnormal levels of a protein marker, from maternal blood sampling.
* Parent carries a genetic translocation, or genetic disease
* Previously affected child or close relative
* Screening in high incident population.

During 1988 a minor revolution in genetic techniques occured, with the capacity to analyse DNA from a single cell using the DNA Polymerase chain reaction (PCR) (Li et al. 1988). In this technique, the single original copy of DNA is multiplied thousands of times by the technique, allowing DNA probing of the sample, within 4-6 hours. The technique is of very broad use in genetic analysis (Mullis 1990). This can be used for preimplantation screening, and is also applicable to CVS. If used after CVS very small samples will be required, allowing screening to be performed at earlier stages in pregnancy. The small sample required will also decrease the chance of miscarriages, and the need for multiple sampling. The only caution, is the need to avoid any contamination of the sample, as a small amount of contaminating DNA can lead to a false result.

The PCR has been used to detect the presence of a Y-chromosomal specific marker in maternal blood samples. In the pilot study it was found to work well, in samples from pregnant women who had gestational ages between 9 to 41 weeks (Lo et al. 1989). This technology has the advantage of ease and is relatively non-invasive. It promises much for further development, and has been further applied (Lo et al. 1990). There is a large number of false positives found in these tests, which is of concern. The consequences of a false positive may mean that an unaffected fetus is aborted. To be sure of the result a larger sample is currently required, because of the effects of contaminating samples (Editorial 1990b).

Preimplantation screening has only begun to be used in 1989, and is still being developed. The first study involved embryos that were not implanted after screening (Handyside et al. 1989), and did not provide any evidence of harm to embryos by the procedure. Another study used DNA from oocytes and the DNA polymerase chain reaction as a model for screening for the gene defect for cystic fibrosis, and found the technique could provide an answer within a few hours (Coutelle et al. 1989). There have been satisfactory tests using mouse embryos, screening for beta-thalassemia (Holding & Monk 1989). One ethical objection, once it is confirmed that it is safe, is that of interference with "nature", by the discarding of diseased embryos, as it is at such an early stage. However, we have established that prevention of disease is an ethical criteria for interference with nature. It is certainly less traumatic than abortion after prenatal diagnosis, at the earliest at 6-8 weeks after conception. However, it might never be widely provided, as it is limited to infertility clinics, and to parents that know that they carry a disease. It might be more ethically acceptable to using abortion, but because it is unlikely to be widely provided, the question of selective abortion must be addressed.

There have been several pregnancies established from embryos that were genetically screened before implantation. The first births were of female babies, selected by the absence of the Y-chromosome, for sex-linked genetic disease (not present in the female). Prior to this clinical use, metabolic studies on biopsed embryos showed that they were normal. The team included Hardy and Handyside (who completed a preliminary genetic study refered to earlier), and the gynaecologist Robert Winston at Hammersmith Hospital, as well as scientists from the University of York (Handyside 1990, Handyside et al. 1990). The actual costs of screening have been estimated at about US$2,500 for each successful pregnancy, which is comparatively low. Given the economic factors that often influence health care decisions, such as the high cost of health care for people suffering from severe diseases, this type of screening may be encouraged by governments. However, it should be stressed that it is still at an experimental stage, and few laboratories have the skills in embryo manipulation.

A possible ethical problem is that this procedure is based on the expectation that more embryos will be made than will be implanted. However, there is not too much difference to normal IVF in which more embryos are fertilised than may be implanted, and any embryo that shows abnormal growth is not implanted. A deeper concern is that this program is genetic selection. Many people support the alleviation of infertility, but a different idea is involved in genetic selection for disease, though it is also often well supported. In all cases that selective abortion is considered ethical, preimplantation diagnosis should also be acceptable, and given the early stages of embryo growth involved, it may be more acceptable. However, the practical problems such as the low success rate of embryo transfer to produce pregnancies, and the higher degree of intrusion for the mother in IVF and embryo transfer compared to selective abortion, mean that this technology is not widely used.

Considering the discussion presented in chapter 5 on the status of the human embryo, it is ethically preferable to have an early abortion, if any at all. In different countries the proportion of early abortions varies. The percentage of total abortions performed before twelve weeks in Denmark and France is 97%, in the USA 92%, and in the U.K. 84% (Gunning 1990). Among the late abortions, a higher proportion will be because of genetic abnormality of the fetus because the screening tests were only able to be performed later in pregnancy. With the use of new technology it is hoped that the number of late abortions will decrease. We should note that in the U.K. about 1% of the abortions are performed for reasons of fetal handicap, certainly a minority of the total.

Genetic Counseling

Genetic counsellors are placed in an increasingly powerful position, but are also increasingly necessary. There needs to be much psychological counseling and information provided to people who are considering prenatal screening. Many parents come after the birth of the first affected child, or in diseases such as Huntington's chorea, where there is possibility of the child being affected.

In a major international survey of genetic counseling (Wertz & Fletcher 1988), it was found that nondirective approaches are preferred by over 90% of the

counsellors. The role of the counsellor is to provide information to allow the parents to make up their mind, rather then imposing any of their own ethical standards on the parents. This widespread acceptance of nondirective counseling means that they act as "decision-facilitators", providing information and leaving decisions up to the patient's autonomy. There is much importance on psychological aspects also, in avoiding anxiety. There are still substantial cultural differences in the responses of counsellors in different countries (Wertz & Fletcher 1989a). There is a more directive approach seen in East Germany or Hungary, or India, where they see it more important to give more advice and guidance (Czeizel 1988) .This has been discussed in the previous chapter. Motulsky (1989) has suggested that the nondirective counseling has been a feature of genetic counseling because it was primarily scientists who developed the services, who unlike physicians, are not in the habit of giving directive advice. This may be one factor, but it is now accepted that nondirective counseling is required to respect the autonomy of the different people who use the services. Many patients, in any country, do expect guidance when making up their minds on difficult questions. It is very important that the easily available testing packages, are accompanied by good counseling.

From the results of Wertz and Fletcher (1989a) the principle concerns of geneticists can be seen. These concerns in order of priority were:

1) Fairness of access to genetic services
2) Abortion choices, and legal restrictions
3) Confidentiality problems
4) Protecting privacy from institutional third parties
5) Disclosure dilemmas
6) Indications for prenatal diagnosis
7) Voluntary or mandatory screening
8) Counseling incapacitated persons

These problems are also discussed in this book. The survey is important as it shows the order of priority seen from practising geneticists. From these factors, a code of ethics was drafted and proposed (Fletcher & Wertz 1990).

The human side of genetic counseling is clearly seen in the study of the proportion of women who would use selective abortion when the chances of the diagnosis being correct are increased. There is a 50% increase in the number who would abort the fetus if the probability of the fetus having a serious neural tube defect increased from 95% to 100% (Faden et al. 1987). This view of certainty versus high chance, a 19 in 20 chance, is interesting. The perception of what is a serious risk varies between patient and counselor, a patient may regard a one in four risk as low, when in fact it is quite high. It is something to do with the type of optimism that we have for things to turn out alright. Other factors found among women who favour selective abortion are those with higher education, those who wanted less children, those who had a previous abortion, and those who attended religious services less often. Women who were in the screening program had a similar attitude to those who were not. Between 60-90% were in favour of selective abortion, depending on the seriousness of the disease.

Public attitudes do change with time, and with counseling. Education increases our understanding of what the benefits may be, and may reduce anxiety about intrusive screening methods. Cultural and religious attitudes are important, and are affected by each societies view of science and the value placed on fetal life.

In an American survey of 2,000 abortion patients, the reasons why women considered abortion were investigated. Only 13% listed as one of the reasons that they were worried that the fetus had a possible health problem, a small proportion (Torres & Forrest 1988).

As with all these medical issues, there is a major ethical problem in the delivery of services. There is unfairness in access to genetic services, and insufficient services to meet needs. This is especially acute for individuals, families and pregnant women who are not referred to genetic services by physicians, who suffer from poverty, and lack of education, or who live far from a genetic centre. The information provided must be of high quality and reliability. There are important psychological skills that are needed, especially after a couple have made their decision (Harper 1988). Whatever the decision is, the couple must be helped to cope with it. There may be feelings of shock, denial, anxiety, anger, guilt, possible depression, relief, reassurance, and various combinations of these.

Because of the explosion of information and possibilities that will be upon us soon, there are calls for a code of ethics of medical genetics to be debated and established (Fletcher & Wertz 1990). There does need to be some international discussion, and the power to sanction those who are unethical. They think that medical geneticists should become more professional in the sense of setting a written ethical code which members must follow. Until now, the arguments are oral or else in the literature. Other reasons for a written code include that the geneticists would be more publicly accountable and their views may be more considered in public policy. A code also enables the moral commitments of this generation to be transmitted to the next generation. What seems the critical question is whether such a code would aid the situation, which it probably would. During the process of deciding on the code it would also make them more aware of the ethical issues, on a broader scale than their daily practise experience. Some may argue that such a code might not be able to change with new technology, however I agree with Wertz and Fletcher that the same basic ethical problems exist. The theme of this book is that genetic engineering is principally a catalyst for us to think about other issues of bioethics.

What Diseases?

A fundamental question, that will need to be addressed in each country, is what genetic diseases can be screened for. In developing countries they may concentrate only on the most prevalent diseases. For example in much of Africa, sickle cell disease is compelling, with 25% of the population of Nigeria carrying the recessive allele for this disease. In Middle Eastern countries, consanguineous marriages are still very common, and this may be the most urgent concern. In developed countries many diseases may be screened for. However, in all countries, there are problems to do with the seriousness of a disease that warrants an abortion. This section also gives some examples of specific diseases that can now be screened for.

The results of genetic screening may pose a dilemma to the parents if the fetus is known to have a genetic defect which will cause disease after birth. They must consider whether induced abortion is a satisfactory "treatment". Views on whether death before birth is preferable to disability after birth vary greatly and they depend on the status given to the human embryo. There are several key questions. Can a

barrier on the slippery slope between severe disease and hair colour be drawn? Should a rigid boundary limit be imposed if it can? In which diseases do we consider no life at all to be desirable to a life of much suffering? It depends on our capacity to treat the disease, for example, can we give them eyeglasses, or a hearing aid, or is it a disease with no treatment.

The problem with fetal screening is that we might not be able to eliminate the disease without eliminating the subject of the disease. We need to answer the question of the status of the embryo? If we take a gradualist view, then we would aim to do screening before the time that we consider abortion unethical. To be morally consistent if the embryo is considered to be of absolute protectable status at a certain time, then if at any period after those dates the living embryo is aborted the death of an embryo is unethical. There are factors of the parents to be considered, but they should not be given priority once the embryo has protectable human status. When detection methods are available for screening at the earlier age then the approach of screening and selective abortion can be ethically used. The exception to this developmental limit might be if the fetus was certain to be destined to die when born.

The issue of embryo status was discussed earlier in chapter 5. An ethical time limit for selective abortion would generally be between the formation of the primitive streak and individualisation at 14 days and the time of brain life. If a fetus has a serious genetic impairment, with a consequence of serious mental deficiency, some people might say that the fetus does not, and will not in the future, have a"life" as "normal" humans have a life. Its potentiality is different. Still many believe potential spiritual relationships are present in all human fetuses. There is an increasing recognition that fetuses should be regarded as the second patient. This will increase as fetal surgery increases. The fetus makes claims for a right to nutrition, protection, and therapy (Blank 1984). The quality of man, the soul, his essence, his unique individuality, with its associated dignity or reverence means that man has a sanctity. However, we should not contend, as some arguments against abortion do, that existence is a good in itself as all other goods depend upon it. Some types of existence are not, and especially if there is no person, then there is no spiritual existence. Abortion is one of the key moral problems in this area, and in some countries it has become a major political issue also.

We must also consider the idea of replacement, by a healthy child, or affects on the family, to ignore these may be to have a negligent view. In a society where we may only have 1-3 children, there is much concern to have healthy children. This is more than in the past where even a century ago, half the children would die, including the weak ones. This type of medical decision is different to the one in a normal doctor-patient relationship, as it concerns the family as a unit.

Some respond by saying that selective abortion is playing God too much, however, they could respond as seeing this is part of a co-creativity with God, and part of our moral responsibility. Some of these diseases may be caused by our industrial pollution, and medical intervention to keep handicapped people alive. These are also human interventions. With some diseases the nutrients that the women has during pregnancy have been linked to birth deformities, such as neural tube defects like spina bifida, this is a more environmental influence. We need further investigation of the causes of disease. However, some argue that we are too ignorant to make these choices, or that the natural order has a certain rightness. If

we use genetic screening it is argued it may be dehumanising, and making children consumer commodities, or damaging to our attitudes to others. However, while there is no reasonable therapy for the sufferers of some disease, there will be strong arguments to allow selective abortion.

About 0.5% of genetic diseases at birth are chromosome abnormalities. There are many different possible chromosomal abnormalities, though most are lethal before birth. The most well known and common survivable chromosomal abnormality is trisomy 21, or Down's syndrome. As discussed, it is the justification given for the chromosomal screening of fetuses of older mothers. Some other abnormalities have a apparently minor affect on individuals, such as an extra Y-chromosome in XYY males.

Some parents of children who have a genetic disease such as Huntington's chorea which acts in later life, may wish their children to be sterilised so that they will not pass on the harmful gene to the next generation. Huntington's chorea is an example of a dominant mutation which causes a dehabilitating disease in the 30's or 40's. Some genetic diseases such as Huntington's or Parkinson's disease only affect the patients after 30-50 years, in fact it is likely that children born now would not have to face the effects of such diseases by the time they are that old, because a therapy will be developed. However, if they are living under the threat of disease it could be very distressing, but the age limit is still better than the life expectancy in some third world countries. Certain families may have wide differences in the age of onset, Huntington's chorea in some families begins in childhood, or after 60 years of age. The symptoms are progressive, and include movement disorder, intellectual decline and psychiatric distress such as depression. There are other common autosomal dominant genetic disorders, for example Marfan syndrome, neurofibromatosis, hypercholesterolemia;. Others also have gene probes available, such as familial amyloidotic polyneuropathy, but are rare, and the severity varies. There are also X-linked dominant genetic disorders.

Genetic screening for Huntington's chorea has been introduced in the last few years, and has raised many of the ethical issues of genetic screening. A genetic marker was found, that could predict 96% chance of developing the disease (Conneally et al. 1984, Wexler 1990). This testing is being performed at about 20 centres in the USA, several in the U.K., and others are beginning in developed countries. Before the test the people know they have a 50% risk, after they will know with high certainty, but with a little doubt. The results of testing of people that have an affected parent will be approximately half positive and half negative. Half the people will know for sure that they are not at risk from the disease and will feel much relief, and the others will know that they carry the harmful gene and until there is effective treatment for the disease, face an early death. There needs to be psychological screening before the genetic screening, so that people with suicidal tendencies are not involved. Some people may prefer to remain in uncertainty, but it is not so easy if their relations have screening. In the unusual case of identical twins, the results will be identical. So if one twin has a result the other can know their verdict. The main problems relate to presymptomatic prediction (Morris et al. 1989).

In most Huntington's chorea screening services, very careful selection of the test subjects is performed. The applicants for testing may come for counseling several times before the decision to test and the information is given. The results are

always given in face-to-face meetings, not over the telephone. Post test counseling must also be sort, and a companion is often required to accompany the person awaiting the result.. Those people who are emotionally unstable are not tested (Wexler 1990). It is essential that such information be accurate, so tests are usually performed twice for confirmation. Because the gene for the disease is not yet isolated, linkage analysis must be used. This requires some samples from family members, making the subject of the services more than just an individual. In this way genetic counseling can involve the family as a unit as well as the individual. Family members who are not themselves afflicted, will still be affected by the presence of the suffering patient in their family. It has been suggested that access to the tests should be conditional on agreement to release their DNA sample for use in other family members who also want the test performed. This is a reasonable request, but should not be used to prevent people using genetic services who do not want others to use their samples.

Because of the nature of presymptomatic testing, it has highlighted more of the ethical problems that arise in genetic screening than some "simpler" cases. Autonomy of the patient requires that the patient can make an informed decision about the procedure. The information must be presented, and the counselor must also examine whether other people are putting pressure on the patient to have the test performed. Beneficience involves the protection of the patient from harm, which in this case may mean those who are emotionally unable to face the results of such a test. Confidentiality is clearly required, and may be difficult in family genetic linkage studies. The principle of justice can be applied so that while there are shortage of resources the most needy are served first (Huggins et al. 1990).

There is the important question of whether we should test children for "adult" genetic diseases. International guidelines have specifically excluded presymptomatic testing of children for this disorder, but there are still many requests from patients, clinicians and adoption agencies to perform tests (Harper & Clarke 1990). The situation may change if the onset of the disease is during childhood, and of course if therapy is available, or lifestyle changes would affect the disease course. In the example of Becker muscular dystrophy, minor symptoms may start in childhood. However, if a child is fatigued it might not be due to this disease, but rather they are just tired. In this case DNA testing of the at risk child could relieve many years of anxiety from their life, they could make normal life plans whereas without the test they might have become pessimistic and depressed, living only with shortterm goals. These benefits need to be balanced against the opposite case, when a child is found positive for the disease and may react very negatively. Medical research with children has many dilemmas (Nicholson 1986).

The testing for Huntington's chorea can also be performed in a nondisclosing prenatal test, so that the risk status of the at-risk parent is not altered, only the risk of the fetus. The DNA from the fetus is tested for the presence of grandparental DNA. The chance of error in the test is about 2%, the rate of recombination between the marker and the unknown gene (Wexler 1990).

There are many new problems regarding the use of such genetic information, as to who owns the information, and if donors of genetic material can control the use of the information in testing of other relations. It can be argued that the test will improve the quality of life of the people who are negative. It is still in the future when the people who are positive can be treated satisfactorily, but it should come

after the gene is studied. Prenatal screening can be used as well as predictive screening for adults. Generally, predictive tests are not considered ethical for children, before they can give their consent and can be considered able to deal with the knowledge. There are also arguments that if the children do know, they can make appropriate career choices if they so wish to.

Some genetic screening tests have been tried on large scale, such as those implemented by the 1972 US National Sickle Cell Anemia Control Act. This provided for research, screening, counseling and education concerning this disease. About one in twelve American Negros carries the allele for sickle cell anemia. There were problems in implementing such a program, as it was seen by some as racist and aimed at slowing down the Negro birth rate. Fortunately the disease can now be treated, so that there are two medical options, one is abortion, the other clinical treatment. Sickle cell diseases (anemia, sickle cell-haemoglobin C and sickle cell-B-thalassemia) affect about 1 in 400 American black newborns. Together with the other haemoglobin disorders they are one of the most common genetic disorders. This situation has recently improved, so that early screening can significantly reduce the rates of morbidity and mortality for the affected individuals, as they are put under better clinical care. They can be given vaccines such as pnemococcal vaccine to reduce the chance of their dying from infection, a common side-effect of these disorders. It is recommended by medical associations to have universal screening of all newborns for hemoglobin disorders, at present using protein analysis, and in the near future using DNA analysis. If a fetus or newborn is found, then the mother will be approached first, to consider whether the family should have screening. Education on screening programs is given in schools, and in the mass media, and will need to expand to give a clearer understanding of the purpose of screening.

Also in USA there have been major screening efforts for other groups at risk, such as Mediterreans for thalassemia, and Ashkenazic Jews for Tay-Sach's disease. Tay-Sach's disease is a rare genetic disease which affects the brain, causing a painful death by 3-4 years age. One in thirty Ashkenazi Jews carry the allele, a ten times higher level than in the general population. When both parents are carriers, the risk of their children being afflicted is one in four. Since it as prevalent in the Jewish community, there have been various screening programs used with the cooperation of the Community. The preference is to screen people before marriage, as the Jewish view is that it is better to prevent marriage than to use prenatal screening and abortion. Premarital testing is more widely accepted than selective abortion. This is slowly being accepted (Merz 1987), and the results can be kept secret to avoid labelling of people and families. Screening has had a major result, as the annual number of new cases in the USA has decreased from 50 to about 10 or 12 annually, though it is not so feasible currently in the United Kingdom due to the low number of Jews, the births are found at a lower level in the general population. There have been major psychological problems with these screening programs, as carriers often are treated, and feel as if they are outcasts. Their have also been real benefits of reducing parental anxiety, and of the adults if they are screened and found not to have the disease. Many can get real peace of mind after years of concern.

One of the most successful prenatal screening programmes of a high risk population has been the diagnosis of beta-thalassemia in Sardinia, Italy. The 15 year program has been based on carrier and prenatal screening. The incidence of homozygous state is 1 in 250 live births in Sardinia, with a carrier rate of 1 in 8,

meaning that about 1 couple in 60 are both carriers, at risk of having a homozygous child. Thalassemia major leads to death by the age of ten. The carrier screening program has detected 30,500 carriers and 1,544 at risk couples, by mid-1990 (Cao 1990). Another 812 couples are known to be at risk because of an affected child, together 87% of the at risk couples in Sardinia know their status. About 90% of possible cases are now prevented by the use of prenatal diagnosis and selective abortion. The population of Sardinia are mainly Catholic, but less than 1% of the couples who were found to have an affected fetus decided not to have an abortion. The reasons for the residual cases of thalassemia were analysed, and it was found that 67% were because of parents ignorance of thalassemia, 13% were for mispaternity, and 20% were for reasons of rejecting abortion. This is very effective screening, and shows the usefulness of an effective carrier screening, prenatal screening, and counseling service in controlling an untreatable genetic disorder. The screening test used CVS followed by DNA amplification and hybridisation, to provide an answer within 24 hours.

Another successful screening program for thalassemia was performed in Cyprus. It was performed with the cooperation of the local church, so that all couples who were getting married were asked to provide certificates showing the alleles that they had. If they were both carriers of thalassemia than they would know that they could use prenatal diagnosis. This represents a good cooperation between geneticists and the church, who were effective agents for the procedure, to reduce the suffering that would otherwise be caused. A similar interaction is being seen with Muslim communities in Britain or the USSR, now that first trimester prenatal screening is available.

In mid-1989 the gene responsible for cystic fibrosis was cloned (Riordan et al. 1989). This allows widespread screening for the known mutation. About 70% of mutations correspond to a specific deletion of three base pairs at amino acid position 508 of the protein (Kerem et al. 1989, Lemna et al. 1990). A simple PCR-based test that allows direct visualization of the result on a stained gel has been described (Ballabio et al. 1990). The American Society of Human Genetics recommended that general screening of the population should wait until other major mutations are identified, and also until there is a better idea of the education and counseling that could be given to cystic fibrosis carriers. There are already commercially operated tests available in the USA, at a cost of about US$ 170 per person (mass screening would be much cheaper). While there is pressure to use new information immediately, there is a general need for a full range of prescreening and followup services to be available for the population to be screened, before a systematic program is introduced. It is also being contemplated in other developed countries, due to it being the most common genetic disorder (affecting about 1 in 1600 live births of Caucasians). The proportional of mutations that correspond to the major mutation is lower in Ashkenazic and Latin families than in Caucasians.

A year after the cystic fibrosis gene and the principle mutation was found the other mutations have proved difficult to find. Another 40 mutations have been described, but these are only found in either one or up to 30 individual cases, so as a total they only account for a few percent of the total. Those mutations often appear only in family groups. Although they contribute to our understanding of the disease, which is still poorly understood, the added complexity delays hopes of a widespread screening service. Individual families may have particular mutations,

and services can be offered to them, but there is pressure to commence general population screening. The major mutation is present in 75% of carriers, which means that 50% of the cystic fibrosis suffering babies (they have the two recessive alleles) could be prenatally detected by a full genetic counseling service. This is still a very high number, but there are reservations about using the screening until it can detect 90% or more of the cases. Among people in Denmark, this mutation comprises 90% of the mutations, but among Ashkenazic Jews and Arabs only 30% of the mutations. However, it may take several years to characterise these other mutations, and should those people at risk wait? As long as there is good counseling and education, the major mutation test should be used as soon as possible to aid the considerable number of couples who will conceive affected fetuses. For example, if one member of a couple is found to carry the major mutation, their spouse could undergo a more detailed genetic testing with the range of probes to other cystic fibrosis gene mutations, as it is not worthwhile to screen the general public for mutations of very low occurrence. Genetic services for those couples who know they are at risk are available in developed countries, so the gene discovery has already been useful in a clinical way, beyond the ability to understand more of the disease and develop better therapies.

An important question is whether it is ethical to use abortion for treatable conditions. An example of this is PKU, which when detected as a newborn, can be treated by dietary measures, with little ill effects, though there is suggestions that there is a higher probability of women with PKU giving birth to retarded children. The people still require special care. A survey has found that most families that have a PKU child would not use prenatal screening on the next fetus, but attitudes may change. If screening is provided it should be funded by medical schemes or insurance so that all could have access. It depends on the age at which it is done. Another complication is that severity of different diseases varies. Some can be treated, such as the continual removal of cancerous tumours caused by neurofibromatosis. On the other side of the line might be short-sightedness that can be corrected with eyeglasses, as that poses very few problems in most societies. Similarly, we may be able to screen for the presence of a normal growth hormone gene, but since adequate therapy is available, it would be unethical to perform prenatal diagnosis for this type of dwarfism. Other diseases, such as albinism, are undesirable, but many people, including Noah (Taylor 1987) suffered from it, and lived otherwise normal lives. The outlooks for an albino are different depending on whether the patient lives in a temperate or tropical climate. If therapy can be begun during fetal life, genetic screening to detect fetuses to be treated is certainly justified.

People tend to be more worried about genetic screening tests for people with mental diseases. An interesting, and sad, story of this type of screening was the case of men who have an extra Y chromosome, called the XYY syndrome. They were imprisoned for long periods if they had this (Beckwith & King 1974), as they were falsely thought to be violent. This screening lead to unfair labelling of people, such as the very weak connection with criminality thought to be associated with the XYY condition. This idea of geneticophobia has been a reason for social discrimination. Many still advocate continued genetic study to see the influence of genes on behaviour, it has important purposes but should be free of any harmful labelling.

There have been different conditions used in the past for judging the sufferers of psychiatric diseases and they have been abused for political purposes. The

problem is that they are often very multifactorial, having a large environmental input. The screening can label some people as unstable, and if the appropriate counseling is not given, then the screening has a negative effect. There are genetic links to several psychiatric disorders, and one would expect many more to be found, as very little research has been done. Psychiatric disorders only receive 6% of the medical research budget in Britain, typical of international medical research priorities. There are genes which appear to lower the environmental threshold to maniac depression, and schizophrenia, and these are being searched for. The actual genes should be sequenced in the coming years, though there may be several. There are several types of cases that come for screening for psychiatric disorders. In some cases people who want to adopt a child come if the child's parents have a psychiatric disorder to see what the chances of the child developing the disorder are. There are also relatives of patient's coming to ask how likely it is that they will develop the disorder, as well as parental screening.

Another dilemma is posed by the finding that there is a strong association between an allele of the gene for dopamine D2 receptor and alcoholism. This discovery must be stressed to be putative, but it illustrates the type of dilemma that our great expansion in genetic knowledge will provide us with. There has been two decades of research which has shown that part of the vulnerability to becoming alcoholic after exposure to alcohol is inherited (Gordis et al. 1990). This has been found by studies of twins, and adopted children, and animal research. In the recent genetic study, 70 brain samples from dead alcoholics and nonalcoholics were used. One allele of the dopamine D2 receptor gene was found in 77% of the alcoholics, but was absent in 72% of the nonalcoholics (Blum et al. 1990). The 70% figure is very high, and was surprising. There is current research being conducted to closely investigate this finding, and other tissue samples can be used since the genotype is the same throughout the body. We must be careful to classify alcoholics in a meaningful way for this sort of study. Understanding how genes and environment interact to lead to alcoholism is a broader challenge. There may be several genes involved, unlike single cell disorders, and several different types of alcoholism may involve different genes. Alcoholism is a common serious disease and may not always be caused by genetic factors. However, many people may be at high risk for it, so we must consider whether we should screen for such alleles if there is some therapy available, or to know who to offer alcoholism prevention schemes to?

There continue to be more diseases that genetic links are found in, such as coronary heart disease (Price et al. 1989), and diseases that markers are found for. Recently a DNA test for type 1 Diabetes was described, where a single substitution in an amino acid of a type of human leukocyte antigen protein is found to increase the chances of developing this type of diabetes by 100-fold (Tcucco et al. 1989). For many diseases there will be many different DNA probes available. Screening for some diseases where the genes are very large will require multiple probes, such as for muscular dystrophy. However, while the gene extends for over two million base pairs, it is possible to test nine mutation hotspot regions simultaneously, to identify deletions and duplications in about 80% of cases (Caskey & McKusick 1990). This illustrates the power of modern technology and how the number of diseases amenable to DNA diagnosis will rapidly expand. In July 1990, the gene for another genetic disease, neurofibromatosis was isolated (Wallace et al. 1990). Neurofibromatosis type 1 is an autosomal dominant disorder affecting 1 in 3500

individuals of most races. It is currently incurable, and varies in severity. The normal gene restrains cell growth in the brain. New mutations have been found to be frequent like Duschenne muscular dystrophy. The gene mutates about one hundred times more frequently than some other genes responsible for genetic diseases. It appears to also cover a large region of the genome, the message is 11 kilobases long, but for the first 4 kilobases found, the exons are distributed over 110 kilobases of genomic DNA, so it likely it is also a very large gene (Cawthon et al. 1990). The gene has been found to contain other genes within it, a new phenomenon. With these types of frequently mutating genes we can envisage an enormous array of results from each sample, even more if it is screened for a variety of diseases.

The types of criteria that are important for parents to consider when reaching a decision include the severity of the disorder and its effect on future life (including life expectancy); the physical, emotional and economic impact on the family; availability of medical management and special facilities to care for the child to be; the reliability of diagnosis and prognosis; effect on society, and the value placed on the human embryo. These decisions will become complex, as the variety of different genetic diseases of varying severities are detectable.

Prenatal Diagnosis Without Abortion

For people who consider abortion always to be unethical, there are still good reasons to use prenatal diagnosis. The procedure may be of significant benefit to both mother and child. Most results will show that the fetus is normal, and so the principle benefit of the test will be to alleviate worry regarding the fetus. This worry can be a significant psychological burden to some mothers and families. The decision regarding abortion should not be considered until after the test results (Clark & DeVore 1989).

If there is found to be an abnormal level of maternal serum AFP, it is usually not due to a neural tube defect, but because of other causes and it can alert the physician to other pregnancy complications. The detection of abnormalities by other tests can significantly alter the care of affected fetuses, and allow them to be born in hospitals where appropriate neonatal care immediately available can positively influence longterm survival and health.

In some circumstances it is better to know that the fetus has a serious genetic abnormality so that should the fetus require very intensive care and put the mother at some risk, then the parents who reject abortion may still consider it best to let the fetus die, to be content with letting nature take its course. If a fetus has a serious abnormality it may still be better to be aware of this before the child is born. The parents can chose to raise the child, and advance knowledge allows them to prepare educationally, emotionally, physically and financially for the caring of the child. There is very little risk attached to prenatal screening and in view of the advantages to the parents and child to be, it should be widely used where available. While we would never see selective abortion as compulsory or as official government policy in a democratic country, when the benefits of prenatal screening are even greater there will be a case for making it standard policy, though because it involves the mother's body, her consent should usually be required.

There can be more direct fetal interventions. The earliest type was the use of blood transfusions to the fetus to treat Rhesus factor incompatibility, which has been

done since the 1960's. Medication can be passed to the fetus indirectly in the mother's bloodstream (for example, biotin). Blood transfusions to the mother to save the life of the fetus have been court-ordered in the USA in some cases where the mother was a Jehovah's witness and rejects the principle of blood transfusion. In the U.K. the law protects the pregnant woman's autonomy. In this case, the courts have overruled the mother's wishes, considering the fetus. It is a difficult area of conflict between mother's autonomy and duties owed to the fetus, and will continue to pose ethical problems. More invasive techniques, such as when direct fetal surgery is possible, using ultrasound and fetoscopy are becoming possible. The surgery can also be performed outside of the mothers' body than the fetus replaced.

Even if the decisions remain voluntary, society can influence the decisions that we make. It could say that it would not provide health care for some "avoidable" diseases, as that is inconsistent with public fairness to health resources, as it may be. Society can publicise the genetic screening much more, or offer incentives. There is a fundamental question of how far to develop alternative therapies, which are often expensive, versus genetic screening. However, some of the conditions that arise in accidents are similar so if the technology overlaps that could be used. There is equal ethical claim to treatment from children whose parents do not use genetic screening, but limits might be placed. When we think of some individual cases where several million dollars have been spent, and the large number of lives that this money could save in the third world especially, we must question priorities. People may talk of protecting a single parent's autonomy while forgetting that 40,000 people die everyday because of malnutrition, and more from preventable diseases that developing countries cannot prevent or treat. There may be less research spent on some serious screenable diseases because they are seen as preventable, but in most cases the same research that discovers the genes that allow screening, also opens the door for research into therapy. Research into rare genetic diseases provides much important basic biological knowledge which can be applied to other problems, so will continue to be seen as important in biomedical research.

However, it would seem to be unethical for the state to refuse to contribute to the care of children who suffer from genetic disease because their parents refused to use genetic screening, as it is unjust to blame the children for their parents actions. It is unlikely that democratic societies would impose selective abortion. In cases of therapy after prenatal screening it is possible, but abortion itself remains controversial. There are economic reasons to favour it, but it still should remain voluntary. There will be more problems when the time arrives when insurance companies include as a criteria for consideration, prenatal screening. If free choice is lost there will be a large cost in human dignity, the main lesson of the enforced eugenic programs as in the United States or Nazi Germany.

Reproductive Choice

The United Nations World Population plan of action declares that "All couples and individuals have a basic right to decide freely and responsibly the number and spacing of their children,". There are several ideas in this statement, and we can find cases where all aspects of it have, and may still be, prevented. Many are conditional

and are prevented in some societies. A question must be, which aspects of reproductive freedom can be limited without violating the basic idea of autonomy.

The right to rear children is conditional on the ability of the parents to look after the child, and not to abuse them. The number of children is limited by very strong policy in some countries, such as Mainland China, because of overpopulation. Different societies have used different criteria to control access to infertility treatments. A current problem is the regulation of AID using "germinal choice", which in many places is not controlled. People can have free choice regarding surrogacy, IVF or AID in some countries such as the USA, but not in others such as West Germany where there is control. Should the law control? The right to have genetic offspring has been made conditional in some time periods with compulsory sterilisation, because of fears of transmission of disease or presumed inability to bear a child, or presumed psychological harm. There is the idea of the right to marry anyone, but has been prevented in some countries, by premarital testing, or making a class of unmarriable individuals, and is subject to family restrictions.

Reproductive freedom is based on the need for bodily-self-determination, or integrity. It is not based on any "right to procreate" itself, but the freedom to determine when, whether and under what conditions we can bear children. A second claim for reproductive freedom for women is because it is predominantly women who must bear the major consequences of pregnancy and raising the child. The interests of the child are a valid part of the argument, even though the person may not yet exist.

The major thrust of the eugenics movement today is in fetal screening and selective abortion (Hubbard 1984). The language has moved to fetal "rights" to health and well-being. The selection criteria has moved from the emphasis on behaviour, to emphasis on health being the major concern. This argument is based on the traditional theme that we should not burden society and successive generations with genetic diseases, as discussed last chapter. Joseph Fletcher (1988) discussed various types of child abuse, including those who preconceptively or prenatally abuse children by "knowingly passing on or risking passing on genetic disease". We have seen the emergence of court cases such as wrongful life, where the fetus is meant to have a "right to health" (Robertson 1983). Some lawyers argue for a position that, while a patient can refuse any medical procedure or treatment, a pregnant woman loses this right if she decides to carry the fetus to term. She is no longer judged to be competent, and some court cases have imposed tort liability on women who fail to use prenatal diagnosis. This is seen by many as a dangerous step back along the road to eugenics. The courts have so far refused to appear to condone abortion, saying it is a question for philosophers whether no life at all is better than a disabled life. Some argue that since the fetus is attached to the mother the choices about treatment should only be made with her informed consent (Fletcher 1979). The US government body set up to examine the question of whether screening (President's Commission 1983), stressed the autonomy of individuals meant that only under the special circumstances of people being unable to protect themselves, could screening be compulsory. The other arguments, such as social utility (economics), allocation of resources evenly, and improving society's "genetic health" are not sufficient to make genetic screening be enforced.

Can Society Limit Genetic Freedom?

We can define genetic freedom as the freedom to bring about the conception of a child with any characters, be they good or bad, or desired or undesired. A fundamental principle of bioethics is autonomy, the freedom of individuals to make decisions regarding their own lives. It is based on the idea that human life is of high value. It is not unconditional freedom, as part of the concept of autonomy must be a recognition of other people's autonomy, or values. Freedom is limited by recognition of other's autonomy to pursue to an equal degree of freedom. There are limits in the way that we should affect other people. The idea of limiting genetic freedom also involves how we treat other people, but people who may not yet exist. There are a few examples of how we already accept limits on behaviour of individuals because of the affect on future people. Pregnant women may be prohibited from certain areas of risk in factories. Foods and drugs are carefully screened to avoid any agents which may cause birth defects.

People are given freedom in their lives, but only as long as they do not prevent others from pursuing an equal degree of freedom, the idea of equality stems from autonomy. In society we should try to maximise the consciousness and participation of individuals, but the social framework of conditions and constraints is not one of individual making. The types of limits that are imposed on people for the benefit of others, called society, includes limits on the noise they can make, the places they can visit, the speed they can move at, and where they can build a house. Inside their house can be protected against others, the idea of privacy, but there are still limits, such as the number of people they can marry, and how they can treat members of their family.

Joseph Fletcher (1988) has argued that reproduction that is planned and controlled is more human than playing "genetic roulette". Humans are distinguished from animals because they have the ability to chose traits. He goes as far as claiming that coital reproduction is less human than laboratory reproduction, as it is more rationally developed. He advocates a shift from accidental or random reproduction to rationally willed reproduction.

Genetic freedom has two sides, on one hand can society say that genetic screening must be used and the disease-causing genes subject to control. If there is some therapy available it may be enforced on children, until they are able to decide themselves, or should it be up to the family. Compulsory genetic screening: is only justified to protect those who can not give their consent, such as for newborn screening for PKU, when there is therapy available. People are given freedom in their lifes, but only as long as they do not prevent others from pursuing an equal degree should have a right to reproductive freedom but does this include genetic freedom? It is the children (who are yet to exist but who can still be considered as individuals) whose genetic freedom should be protected from influence that limits choices, within the framework of a healthy life.

Genetic counseling aimed at the immediate family can be very successful, but on the wider societal level for eugenic goals it may not be. It can have some affect, for instance in 1988 the proportion of Down's syndrome babies born in the United Kingdom was a quarter less than that before screening, due to the widespread use of fetal screening and selective abortion of afflicted fetuses. This screening has no eugenic outcome in the gene pool, as the sufferers of the disease are sterile and can not reproduce, however, it has had an affect on many potential families. It has been

routine to use amniocentesis screening of pregnant women over 35 years old, as they have a greater chance of chromosome trisomies such as Down's syndrome (trisomy 21, three copies of the chromosome number 21 are present). The risk increases with age. If used on the total population than because of the risks of miscarriage after CVS or amniocentesis, than more fetuses would be lost then detected. The figures in the United States would be approximately 2,000 fetuses miscarried, and 1,000 fetuses detected with Down's syndrome. However, if incorporating screening for multiple disorders from the single sample, then the result would be better. The risk of miscarriage is 1% loss, is negligible compared to the 70-80% loss from conception, as far as numbers go. It depends on the fetal age. There are new methods for maternal blood testing (Wald et al. 1988), as a preliminary screening test which should increase the number of fetuses that can be examined, and will make it possible to offer the technique to younger women.

Compelled medical treatment of pregnant women is generally not ethical. Society may gain more by allowing each pregnant woman to live as seems good to her rather than by compelling certain screening or fetal therapy (Nelson & Milliken 1988). Voluntary measures are better to protect the body, this is different to decisions made directly because of desired characteristics in the fetus. There has been much controversy surrounding enforced caesareans in USA, which are not possible in Britain, and there have been women who have run away from hospitals due to this, placing themselves and the child at greater danger. Many of these cases end up giving birth in the natural way, with good results, which calls into question the necessity of the court order. In a April 1990 Washington D.C. Appeal Court decision, the court upheld by 7 votes to 1, that a pregnant woman may not be forced to undergo a caesarean section to save her fetus (Brahams 1990). This may help prevent the practise in the USA of overriding the mother's interests. In the USA there is a very high number of caesarians performed (Evans 1988).

The greater use of prenatal genetic screening will highlight this problem. There are two types of case, one is when there is some therapy for the affliction that should be begun before birth. Then there are some grounds for enforcing some types of treatment, such as blood transfusions. There have been women put in prison to prevent them taking drugs during pregnancy. There is much legal debate in the USA. The other is when there is no therapy, and the prefered course by the family medical insurance company is for selective abortion. This is a key issue, and one which will be discussed later, but currently courts are unwilling to condone abortion and it will not occur in societies that recognise the autonomy of mothers or some right to life of a fetus. If there is no therapy then society cannot ethically enforce abortion, but it can control the application of medical resources in a national health service.

We must accept that human beings are conceived in a very risky way, with a greater chance of genetic disease than any other species. We also all need to accept that we all die, and will suffer. The question whether a human life involving genetic suffering is one which is not worth living will remain an unanswerable decision, and so must be left up to individual cases. We can seek therapy, and there is an obligation to seek therapy, but there is no obligation to kill other creatures if they suffer, only sometimes, to let them die. We need to let autonomy dominate in order to avoid any future societal abuse, this has also been called in the US the "Right to privacy", a right to be left alone regarding decisions to bear a child. However, there

are many external pressures that will push couples to use genetic screening and selective abortion. These include the willingness of society to care for the sick, which is often lacking. People may shun those who did not abort a child who suffers from genetic disease. The underlying values of society need to be changed to avoid problems, and while we should strive for this goal, we have to be pessimistic. The laws in some countries, such as Sweden and the USA, to protect handicapped people from employment discrimination are useful, but fully nationally funded health and education systems are the minimum ethical duties that societies must use to change the situation.

On the otherhand can society allow individuals to have free choice over the use of genetic manipulation when there is no medical reason for it? Such as nonmedical sex selection, which may have some cultural reason but a reason that is based on inequality, or something such as hair colour which is just a passing whim of the parents.

Sex Selection

There are various possible techniques for sex selection (Bennett 1983, President's Commission 1983, Warren 1985), though this has been officially limited to use for parents who are carriers of a sex-linked genetic disease. This type of disease prevention is different to the general question, and includes diseases such as haemophilia and muscular dystrophy when carried by the woman, will affect only male offspring. Sex selection is a precedent for genetic screening for characters that have nothing to do with disease so it is interesting to ask what attitudes genetic counsellors and the public have to it.

There are preconception methods, arising from the study of sperm formation and the factors that influence it. There are various manipulations of the movement of the sperm within the vaginal tract, such as the presence of antibodies in the vaginal tract, and the slightly different motilities of sperm containing the X or Y chromosomes, and artificial insemination with specially treated semen. Y-chromosome carrying sperm are 3% lighter than X-bearing sperm. Methods that have been used to separate sperm, including separation by mass, electric charge or staining are not very successful. There has been a method using differential binding to a protein solution, which can increase the chance of having a male to 75%. A company called Gametrics claims that after 600 births using their treated sperm, 75% were male (Ericsson 1988). There are also dietary methods that have been suggested. The methods do not seem to present any harm to the offspring as a result of the technique. There is much research in these techniques as they have many uses in agriculture, where a female calf can be worth ten times more than a male. The primary postconception method is fetal screening and selective abortion. It is possible to sex a single cell using embryo biopsy or preimplantation diagnosis, which may have more immediate use in agriculture. There have also been methods developed to identify male and female embryos by specific sex-linked antibodies. In the near future it will be possible to use maternal blood sampling for sex determination. While sex selection has less problems if done before conception, there are still major objections.

In many countries of the world, feminicide is practised. It is a dangerous precedent to allow sex selection to be part of reproductive choice. The current technology allows routine screening at 9-11 weeks by ultrasound, or the earlier use

of the more invasive technique of CVS. Fetal chromosome analysis through maternal blood sampling may be available, as well as preconception methods. The attitudes of doctors to allowing sex selective abortions varies between different countries. In certain cases the physicians in countries such as the USA would comply with requests for prenatal sex selection. In a case where a couple with four healthy daughters wants a son, and will abort the fetus if it is female or if there is no diagnosis, many would comply with this request. In a 1985 survey, the percentage of genetic counselors that would comply in various countries were, USA 62%, Hungary 60%, Canada 47%, Sweden 38%, Israel 33%, Brazil 30%, Greece 29%, United Kingdom 24%. Most argued that they would do it out of respect for the patient's autonomy and rights of choice, only in Hungary did they add the threat of abortion as being significant (Wertz & Fletcher 1989a). The trend over time is to be more tolerant of sex selection, perhaps extending the other trends of control over pregnancy and birth of children.

Arguments against sex selection include the fact that being a particular sex is not a disease, if it was used it could lead to social inequality between the sexes, it is not a sufficient reason for abortion, and it is a waste of resources as there are many genuine cases to deal with. The two major arguments for sex selection are that it is individual liberty, and that it may reduce population growth in countries where people try to have a male and will continue to have children until they do. When having smaller families there is greater pressure for sex selection, but it should still be resisted. Warren (1985) examined the claims that sex selection would enhance the quality of life of child and family, however there is no evidence and probably more against it. It could lead to marital conflict if the parents have different ideas. In the end, sex selection is inherently sexist and it believes that different sexes are unequal. Even if prenatal diagnosis became common for all, it will still be objectionable as it undermines the major moral reason that justifies prenatal diagnosis and selective abortion - the prevention of serious genetic disease (Wertz & Fletcher 1989b).

Sex is one character that is not a disease, as are others such as height, eye and hair colour, and skin colour. Many parents include some of these characters when they think of their ideal child also. Sex selection would set a precedent for the near future, as the number of testable characters increases. It is important to take a stand now against this growing trend. It may be better to avoid making many reproductive laws, but it may still be necessary if genetic counseling and information can not control the abuse of selective abortion. A simple method is to withhold the information of fetal sex,which is already done in some clinics. It is a case where directive counseling is required, and possibly legal control.

Genetic Selection for Nondisease Should be Illegal

In the current situation we could use the argument that genetic screening should not be performed for nondisease conditions as there is a shortage of resources already (Fletcher 1988a). In some countries, money can buy anything, including many unnecessary medical resources, we can also say that this is wrong in a world, or even country, where many people do not get adequate medical resources. This is something that should be applicable to all of medicine, and both cases are wrong, despite what capitalism likes to say. We should direct scientific efforts towards treatment and prevention of serious diseases away from trivial pursuits. It will be useful if genetic counselors do refuse to offer their services for

this reason, but it still begs the underlying question. If resources were available would it be ethical?

We can make the situation easier if we consider there is no risk involved in the process, no abortion required, but preconception control? There is still a dilemma to be faced. These three arguments will eventually not be significant, and they are not applicable for some existing methods.

One view is that there is no difference between altering genes, and the variability in the environment that parents can subject children to. However, we can argue that the danger in this is that this would limit something we could call the natural autonomy of the new individuals. This would introduce the concept of a "natural genetic autonomy", the freedom to let the genes come together naturally and to let that individual develop their genetic potential without unnecessary interference by parents or society. While we may give freedom to nurture children in various ways, there are imposed limits.

It has been argued by some that present nonexistence of future persons entails that obligations we have towards them are not based on rights. However, the present non-existence of future persons is not an impediment to the attribution of rights to them (Elliot 1989).

Parental concern with chosing characters of children is incompatible with the attitude of unconditional acceptance that is found to be essential to good parenting. The more a child's genome is subject to manipulation, and is a result of the choices of others, the more we can consider children to be a social product, no longer unique persons. Society needs to promote good attitudes to children and the family.

The family is the natural and fundamental unit of society and is entitled to protection. It is a fundamental human right. In the USA there is a very strong "rights" movement, and the value orientation of most gives preeminence to the right to procreate (Blank 1984). The new technology may lead to a move away from this. There is increasing consideration given to fetal rights and the rights of the child. This is reflected in the recent decisions of the US Supreme Court, in the Webster case which limits access to abortion, and other related decisions. We may need to promote "family rights", to protect the interests of the family.

The basic justifications that are used to limit reproductive choice are paternalism, the public health, and economics. Paternalism is the protection of others against the effects of their own "wrong" decisions; but that should not enforce behaviour in people able to make a balanced decision. We should be responsible in our own behaviour, but we can not enforce others to follow our own values. The exceptions will be those who are mentally incompetent. The public health and economic arguments are much less justifiable reasons, especially in the world where so much government money is spend on military spending. Society has little moral weight to enforce behaviour change on others, until they have eliminated many factors which damage health and misuse money. There can be no moral superiority to a society which spends on the military but refuses to spend on the sick or poor.

There is another argument that if we let society or parents chose characters in their children then it will have a harmful affect on social attitudes to people who fail to meet those characteristics. A problem with the increasing availability of genetic screening is that while it can help people have children free of known genetic defects, it makes life more difficult for many parents and their children who suffer

from the disease, who did not use screening. It may increasingly be seen as not an act of fate but the parents' fault (Hubbard 1986). Modern society is moving towards viewing reproduction as a commodity, producing a luxury item, a newborn child free of defect. It may make people less tolerant of the variety of human beings. In the case of sex selection it represents prejudicial attitudes which are inappropriate in a world where we are trying to get rid of such prejudice.

Opponents of social control of genetic screening argue that if we promote selective abortion against sufferers of a particular genetic disease, our attitude to handicapped people will change. These ideas can be philosophically separated, but in some people's minds they are connected. The social affects of a technique are often far-reaching, and so we should be cautious regarding ideas which could lead to eugenic discrimination. We should remember the concept of charity, or agape, which they introduced to Western medicine in the third century from Christianity, and which has been with us since. We can never eradicate genetic disease, as there are always mutations occuring. The aim of research into genetics is not primarily to eradicate them but for therapy. Some countries have taken steps towards the compulsory genetic screening of individuals before they can marry. We can learn some lessons also from the screening processes that are being used on AIDS sufferers, the discrimination that they face, and the growing recognition of the protection from discrimination that they need. One USA state, Illinois, had a policy for mandatory premarital testing for HIV virus, and couples wishing to be married had to submit to this test, or else get married in a neighbouring state. The idea is that the spouse should know if the partner has HIV, and the public health motivation was to slow the spread of HIV. However, it is ethically unacceptable to enforce such screening. A more practical problem was found with this testing program, the cost. The cost was worked out to be US$320,000 per individual identified with HIV, which would possibly avoid a similar number of individuals becoming HIV positive. This is very cost inefficient. In New York city, such a program was rejected prior to use for this ineffective use of resources. Such mandatory screening programs are ineffective ways to combat disease, and we need to remember this example when considering genetic disease screening. An older example was mandatory premarital screening for syphilis. In 1958, a comparison of 9 states without a compulsory law, and 30 states with a compulsory law for premarital syphilis testing, showed that the decrease in syphilis was the same in both states. Actually 21 states still have such laws, they are difficult to remove from the statutes once there (Silverman 1990). Nevertheless, we do have some genetic responsibility to our offspring if the techniques are available. If we have the option of screening a fetus before it is a person, or ourselves before marriage and procreation, than we should value the technology, and use it wisely. It has the potential to be used to enrich lives if not abused, but it should be voluntary. Education about diseases and risks is the most important goal.

There is the argument of reducing genetic variability, but it is doubtful as to whether this sort of selection would really have much affect biologically. The major affect is on reduced social variability. If we want to maintain or should we say develop a society where people's autonomy is respected then we should not allow the acceptance of genetic restrictions on nondisease characteristics. This means that society could for the benefit of society, and protecting its members from developing narrow views whether they be sexist or intelligence seeking, restrict the freedom of

individuals to use techniques to affect the children. We already limit the environmental freedom of parents, we also need to limit their genetic freedom to chose.

The President's Commission (1983) and others have recommended that public policy should discourage sex selection but that it should not be a legal prohibition. One of the major reasons given was that it would be impractical. However, a legal prohibition may be quite possible, by withholding information on the sex of the fetus during genetic counseling. Wertz and Fletcher (1989a) argue against a legal prohibition, unless attitudes in a particular country make it the only means to prevent it. There is a desire not to create many laws connected with reproductive decisions, which is fine, as long as it works in practise. A similar principle will be needed for other nondisease characters. At least national and international medical organisations should make strong stands that their members should follow.

Society has some role in reproductive control. This represents a tension between the individual and society, however it is consistent with justice, fairness, autonomy of future generations. There is a tension between human liberty and responsibility of individuals (Dunstan 1988). It is not based on a fear of changing the genes themselves, but can be argued in view of the protection of society's social behaviour. We should direct science and medicine towards the treatment and prevention of disease, and sex selection or AID for germinal choice are two current techniques which set a dangerous precedent for future tinkering, and move away from the goals of our society. We need to decide the goals of society and adjust technology to them. As a social morality grows out of the tension between personal and social interests, we need to take account of the broader social consequences of clinical decisions made primarily in the interests of individual patients. There are more important arguments based on the effects of individuals upon society. Physicians or genetic counsellors are not merely technicians to aid the pursuit of their patient's desires, they need to be constrained within social policy, responsible ethically and clinically for the procedure's outcome.

We must apply caution in the use of genetic screening. As we saw in the last chapter, over enthusiasm with genetics led to widespread acceptance of eugenics. This euphoria was not even supported by much real science. The social influences that the future programs will have is very large. We may need to advance our social attitudes before introducing such systems.

Privacy of Genetic Information

There will be many medical advantages from the increased ability for genetic screening. Many individuals will be identified that carry genetic disease, and appropriate therapy given to them or their progeny. There will be a dramatic increase in the amount of patient genetic data that can be collected. The number of human genes that are sequenced is exponentially increasing, in 1982 only 22 were known, by 1984 there were 132, by 1989 we have over 5,000 human gene sequences. The total human genome sequence might be available within a decade. This raises many questions regarding the rights of individual privacy, regarding what information others can have access to. This will be a key issue for the future as so many

diseases, or genes, will be able to be screened for. The type of information that can be screened for covers blood type, tissue type, to predisposition to diseases, or the certainty of knowing that a late acting disease will come. They may reveal important hints on a person's physical or intellectual potential.

The data can play an important role in the life of the individual, affecting the choice of spouse, psychological health, reproductive decisions such as whether to have children, and whether to use prenatal screening and selective abortion or therapy. There will have to be decisions regarding personal health risks which may be affected by diet, smoking, etc., and the type of work. There may also need to be decisions regarding insurance schemes, and retirement. The genetic information can be of great benefit to the individual person to know about their genetic constitution. However, there can be great risk involved if other people obtain it (Zimmerli 1990). While screening for susceptability to lung disease if exposed to asbestos might be an advantage if an alternative job in the company can be found, it has already been used to prevent people from working in some factories (Nelkin & Tancred 1989, Holtzman 1989).

There are two different technologies for genetic testing. Genetic screening can be used to identify people who are susceptible to certain illnesses. Genetic monitoring is different, it is aimed at understanding the significance of genetic mutations that occur in groups of people as a result of exposure to chemicals (Murray 1985). Gene monitoring is targeted at a group, to determine whether a carcinogen is present in the workplace.

Genetic screening targeted at individuals can be used as an effective exclusionary tool (Rowin 1988). It may become an excuse for companies not to hire susceptible workers, or women of child-bearing age, instead of cleaning up the factory. It is a major problem ethically to decide if insurance companies are entitled to genetically screen potential clients. Some employers screen for sensitivity to some pollutants present in the factory, such as genetic predisposition to cancer if there are carcinogens present. What is ironic is that genetic screening may exclude some workers, who will be more suited to other aspects of the work. Some workers will be hired whose genetic weaknesses have yet to be determined. This screening is regardless of the more important occupational suitability for each job (Weiss 1989). This also interferes with rights of people to chose (Harsanyi & Hutton 1982). On the otherhand, if a person suffers from hemophilia it would be wrong not to warn them of the risks of becoming a butcher (Motulsky 1989). Employers also offer insurance schemes, which in some countries are the best systems for health care available. The U.S. law states that companies can not discharge an employee for the purposes of reducing their benefit costs. In July 1990 a new law was passed to outlaw employers from discriminating on the basis of handicap. This is of major importance, and some lawyers believe it extends to genetic disease. Before this employers could refuse to hire on the basis of medical and genetic findings, unless they were in a state that had specific laws. In New Jersey there is a specific prohibition on discrimination based on an individual's atypical cellular or blood trait (Rowan 1989). If an employer is receiving Federal financial assistance, that employer may not make preemployment inquiry about whether the applicant is handicapped, unless all candidates are required to have such a medical examination. This means that a general genetic screening could be performed, unless new laws prevent it, as in the case of New Jersey. In Britain, the

law does not protect against genetic discrimination, and if a person lies about the results of a genetic test they can be dismissed from their employment. International law is required, as well as a change in society.

There are diseases such as Huntington's chorea which will mean people have to retire early, and will require payment of insurance or pensions, so companies, and even governments, have required information from people. If they carry the gene they can not get the job, or maybe cannot be insured. They may not be able to get a morgage if they have increased risk to psychiatric diseases. There will have to be guidelines on the availability of such information. It is not the same as AIDS, which itself is not normally contagious, as these diseases have no public health risk. In the cases were a disease is noncommunicable, the only other people at risk are the progeny.

Closely related individuals may share the disorder, so if one is tested the others will get a hint. There are important ethical and legal questions concerning the relatives of test subjects. There are issues of confidentiality. Respect for confidentiality is one of the key principles in the development of genetic screening programs. Genetic diagnostic information must be held strictly confidential. The only exception is when another family member needs to know the information because of a direct medical risk that would be averted if the information is known. If a person is found to be positive, will relatives be warned of their risk? Is there a right to know, and a right not to know? If genetic registrars are established, should relatives be involved in deciding whether one member of the families' data can be recorded, as the information could be used to affect other family members as well as that individual?

It may be very difficult to protect individual that do not want to know from learning of "bad" news from their relative's test results. However it may be done, it is one thing to maintain privacy, and another to aways tell the truth. A similar dilemma often arises in the case of nonpaternity, the genetic father is not the husband of the woman. A very limited amount of paternalism, in the sense of considering the adverse consequences of revealing the information, may be justified. With presymptomatic screening, the problem is avoided if psychological screening is completed before any genetic information is obtained, but it is not aways possible. Huntington's chorea, colonic polyposis and polycystic kidney disease may not be expressed until middle or old age, the information can predict the future health of the person. There are many emotional problems, as with AIDS screening, for those people. In studies and counseling of patients that have had predictive testing for Huntington's chorea, among the people given a positive answer, about 20% of them did not accept the conclusion and believed that they would not get the disease. If the counseling is good, and patients are screened psychologically before testing, than there is little evidence to support the idea that they will commit suicide. However, if people are not considered able to take the bad news, than they should not be tested. Of course some people will be negative too, which may relieve much anxiety from their lives, allowing them to marry and have children which in some cases they would not of done before the testing.

If people are going to benefit from the information provided by genetic screening there must be no stigma attached to carry a potential disease causing allele. The people may be branded if they carry a disease. Our society tends to brand people into a positive or negative category if they suffer from some affliction. A

sign of disability can be very detrimental to future life prospects. New technology will provide the information about disease susceptability, but they can not determine a moral choice. The type of decisions that depend on genetic data involve the most personal decisions concerning people's lives, such as the choice of spouse, reproduction decisions, personal health habits, financial and insurance, and retirement decisions (OTA 1984). Decisions regarding life choices should be left to the individuals concerned, with as much counseling aid as possible. The screening should be accessible to all, to be fair (President's Commission 1983). Rather than this new technology making us more mechanistic, the best approach will need to be much more community support and love for our neighbour than before. In a just society there are no justifications for genetic discrimination, only therapy.

There are many benefits to insurance companies and to the general public economically, from knowledge of people's genetic data. Insurance companies costs can be lowered, to make them more competitive, if using genetic testing. If it is not stopped at this early stage it will lead to much discrimination. In a few cases predictive genetic testing can allow individuals currently unable to get insurance because of family history of disease, to get insurance. If society wants to be just it will have to make a rule that there is no genetic discrimination. To select for smoking habits, or for dietary differences may be fairer, as people can chose to lower the risks associated with bad habits; however, it is unfair to discriminate on the basis of what is something over which people have no control, their genes. There may be genetic susceptability to alcoholism, and it is possible even smoking has deeper roots than personal choices. These possibilities pose future ethical dilemmas about treatment, environmental, social therapy and genetic therapy may all be used. It would have to be a general rule so that all the insurance companies shared the cost. In the early 1970's some U.S. insurance companies charged blacks, who were carriers of sickle cell diseases, higher rates, even though they are at no risk from the disease. There is less discrimination for carriers currently, but still some. There is a list of diseases for which some insurance companies will not insure sufferers for, including sickle cell anemia, Huntington's chorea, insulin-dependent diabetes, muscular dystrophy, and many more (Holtzman 1988). However, these screening tests are not routinely requested, but many insurance companies use tests for HIV infection, and reject the positive applicants. In several states (Florida, Maryland, North Carolina) sickle cell disease allele carriers are protected by laws preventing insurance companies discriminating against them, though this is not for those who suffer from the disease. In a few U.S. states there are so-called high risk pools, which are available to help those people who are uninsurable. State-regulated insurance companies are required to pay into the pool, but it is better to have premiums shared among all, or a national health service (Holtzman 1989). It is certainly more ethical. Group medical insurance, which covers about 85% of US citizens, is offered to particular employment groups and usually does not consider health risks of the individual applicants, so that access to patient genetic data is not necessary. However, the agreement signed when entering some group schemes may allow unrestricted access to their health records, which could be used (OTA 1984).

The procedures that are used by insurance companies and employers are generally a questionnaire, and physical examination. The physical examination may include blood and urine analysis. The doctors may test for the presence of different

drugs, both drugs such as nicotine and cocaine, and prescription drugs taken for different medical conditions. In the USA more than half those seeking employment must undergo a physical examination, and it is especially common in larger companies. Employers in the USA have a federal law which protects the handicapped from employment discrimination. It is also general practise not to screen for HIV infection by employers. As the costs of AIDS treatment rises, it is likely that more companies will screen for it, unless a law prevents them from this. It is unlikely that the employers will offer general genetic screening tests in the immediate future, only in specific industries. If an easy genetic test becomes available it may be tempting to use it, so laws to prevent discrimination should be enacted to prevent this. It is also important to ensure that any testing which is done, is accurate with very low probability of false positive tests.

In certain cases there may be a duty to know genetic information if a third party might be harmed. If children are born, then this could save them from a disease. For some diseases, certain types of employment should be avoided. For instance when people start to suffer from Huntington's chorea they can have losses of concentration for a few seconds or longer. If they are an air traffic controller, or pilot, or quality control worker in a factory, then this could have serious consequences for others. Should screening be compulsory for sensitive areas, possibly? However, there needs to be information protection. The issue is whether "pre-clinical diagnosis" should be used, as the worker may still have twenty years normal work with no clinical condition. There will also be potential spouses, which are also third parties that should know. However, numerous studies of the ethical principles to follow when genetic screening recommend that mandatory genetic screening programs are only justified when voluntary testing proves inadequate to prevent serious harm to the defenseless, such as children, that could be avoided were screening performed (President's Commission 1983).

An important parallel is being seen with compulsory drug testing of federal employees in the USA. Workers from groups such as fire fighters, police officers, school bus aides, and computer programmers have been subjected to mandatory drug testing. In the U.S. Constitution, the fourth amendment forbids unreasonable searches of individuals. It is agreed that a blood, urine or breath test constitutes a search. What has been disputed is whether it is reasonable to search people without any suspicion of guilt. The U.S. Supreme Court has supported mandatory searches in the case of railroad workers and Custom's service employees, for utilitarian reasons (Glantz 1989). However, there has been much criticism of these and similar decisions as they infringe individual liberties. The test results were not even available to those who were tested. If it becomes accepted practice, then it is likely to be extended to genetic tests, when it is seen to benefit the public good.

Recently, several private companies, such as bus tour operators, have used a computer based performance test as a measure of the capacity of the employees to concentrate. The test involves keeping a marker on a computer screen in one place as the computer tries to move it around. If the employees cannot do this they will be sent home that day, but no enquiry is made into whether they are emotionally upset, or under the influence of alcohol or drugs. In this way respecting their privacy. The test looks only at the symptoms that affect others. There are related issues to those found with Huntington's chorea, described above, in screening for causes presymtomatically.

Genetic patient data are different from other types of disease-related medical information. In contrast to communicable disease, the public at large is not at risk of contracting genetic disease, only potential children. With contagious diseases the issue of public health may override some of the protections normally given to individuals. Future individuals do have some interest in the data. Closely-related individuals may be directly affected by the knowledge, and vice versa; which may be a benefit, or an unwanted burden. Pre-clinical prediction provides a look at the future health of an individual. The awareness of a disease with no cure can be an unnecessary emotional burden to give to people.

Confidentiality is a long-standing principle of good medical ethics. It is considered essential to maintaining a good doctor-patient relationship. If the patient does not trust the doctor, than they may not reveal delicate health issues to the doctor. Only if a third party is in serious risk may a doctor consider breaching confidentiality. Another argument for the maintenance of confidentiality is from the rights of the patient. For example a sample of the patients' tissue may be collected and used for tests, but this should only be done with their consent. Consent to use tissue for one test does not mean consent for other tests, unless specifically stated, though in practise it consent for all tests is not sought.

Genetic research also involves necessary contributions from the public, in both the donation of samples and the provision of information. If we expect to benefit from medicine it is good for all to contribute if needed, as it may directly benefit us in the future, and we have all benefitted indirectly from medical research during our lives. The issue of who owns patients' data is a current question in the some countries. The U.K. Government has proposed the total computerisation of National Health Service general practice records. This will improve efficiency, but it will also create a vast store of potentially valuable data. The data is being anonymised and sold to private companies in return for computers given to the general practitioners to use. The data can be used in research, for public interest, or for private gain (Brahams 1990). The patients' data is effectively sold to private companies, though confidentiality is not breached as long as it is ensured to be anonymous. In New Zealand similar projects are underway. One example involves the results of about 4,000 patients who have, and are being treated for hypertension, to compare their drug treatments. One drug company wants to test their own drug's performance in this system. It is legally uncertain whose data it actually is, though if anonymous, it can be argued that given the potential benefits from the information arising from studies of the data, it may be ethically acceptable.

It is one thing to provide data, but another to provide DNA samples. There are different DNA banks that have been created in many genetic clinics. There are guidelines which detail some of the precautions that should be made in these banks. The purpose of DNA banks is to provide for the future requirements of those families that gave the samples. Verbal consent is required from all people donating samples for research use (Yates et al. 1989). One criteria for the release of samples or information is that nonidentifying information could be released given prospects of general benefit, but identifying information should only be given with the consent of the donor (Zimmerli 1990).

There have been some publications that have deliberately changed family pedigrees to prevent relatives finding out information regarding there status, such as whether they have Huntington's disease alleles. While this is good to protect

people's right to know, and right not to know, it must be very clearly noted in any paper that this is done. Otherwise, people may not be able to do future research, for some association with sex or age for instance, that may be useful in elucidating the disease. The original data should be stored in some repository so that researchers can apply for it. For example, a Venezelean Huntington's disease family pedigree collected by international researchers involves over 8,000 individuals, which is a very important resource for other genetic researchers, now and in the future in the study of other genes. There is a balance that can be maintained to ensure both privacy, and scientific integrity.

There is also the question of where actual samples of DNA should be held, and if these should be ever used without consent of the donors. It may be impossible if the donor has died, but the children, who share half the genes, must have some claim on the material also. It is a difficult issue, and represents the unique nature of genetic material. It is intergenerational in nature.

DNA Fingerprinting

Another area where genetic information is increasingly used is in legal cases. The technology used is DNA fingerprinting. Most DNA fingerprinting involve comparing different restriction fragment length polymorphisms (RFLPs). Forensic science has begun to use these to study small samples of blood or semen from criminal cases to match up with suspects. The samples can be amplified by the Polymerase Chain reaction (PCR) so very small samples are needed. There has been recent controversy regarding the random probability of the matching, and the lack of scientific method used in some cases. The guidelines need to be clarified (Lander 1989). The probability of finding the same sample in the population is often exaggerated as the values are based on random mating, which is not what is found in most population and racial groups (Joyce 1990). People tend to marry within particular groups rather than in the general population.

There are still technical difficulties in analysis, such as correction for band-shifting which arises in 30% of DNA fingerprinting cases. The same bands may be detected in two samples, but the pattern may be displaced in one direction compared to the other because of other compounds in the sample. The contaminants may include bacteria, detergents, drugs and dirt, as well as DNA from other humans or animals. It is possible for sunlight or oxygen in the air to cause changes in DNA, which means we must be careful in the collection of very small starting samples. The DNA prints from the same individual may look identical, or patterns from the same individual may look dissimilar. The bands may be smudgy and smeared, which makes it difficult to tell where one band starts and another ends. By using standard markers it is possible to compare the samples. The scientific basis is well established, but the practice has been found poor in some cases (Norman 1989, Knight 1990).

Approximately half of each DNA fingerprint is inherited from each parent. Comparison of the parent's and child's DNA fingerprints can reveal the real genetic relationships. The evidence is accepted in many countries for criminal cases, and also in disputed paternity cases for immigration purposes. The technique can also be used to identify bodies that are otherwise unidentifiable. It can also be used for

tissue transplantation matching.

The actual testing may be performed by commercial laboratories, under commission from government police departments. In Europe there is a standardised technique, using the same restriction endonuclease (*Hinf*I) and two standard chemical probes for DNA identification. The probes used are Cellmark's MS43A and Promega's YNH24. Laboratories can use a variety of other probes for further clarification if required, after these two are used. The U.S. Congress may introduce legislation to stipulate standard technical procedures for commercial companies (Thompson & Ford 1990). Currently, the U.S. Fedral Bureau of Investigation's standard is *Hae*III. There may still be room for improvement, so it may be best to postpone any legislation, but standardisation is desirable. The laboratories are subject to blind testing, any only those which maintain good results on these samples are officially used.

There are civil liberties problems, as mentioned earlier. It has been proposed that DNA fingerprints from all criminals be stored, as fingerprints are already. This would establish a database to be screened for police investigations. It will be feasible to do this later in this decade when the techniques have been standardised. It may aid forensic science sufficiently to be worth the cost in "liberty", as long as the database was used according to strict criteria to prevent abuse (Ballantyne et al. 1989).

If we consider individual human life to be of a high status, than we should protect individuals from discrimination. Some access to personal information will be required for medical emergencies, but otherwise third parties should not have any access. A just society must carry the cost of caring for the sick, as it has since the revolution in caring for the sick in the second and third centuries A.D. This will mean sharing out the cost of health insurance, and disability pensions, as in the past. This issue is very important, more than some of the other issues that grab our attention from new genetic technologies. The law must protect privacy of genetic information, as the alternative is widespread discrimination of many people.

The call is for any employer or insurer not to discriminate. Government action will be required. Genetic discrimination has joined, racial, sexual and religious discrimination. Knowledge obtained by genetic screening, at gene level or at the level of DNA fingerprinting, will be very powerful. We must be wise in our use of it. Like much offered by science, it has the power to enrich lives as well as to frustrate or destroy them.

14. Human Gene Therapy

Gene Therapy is Another Medical Therapy

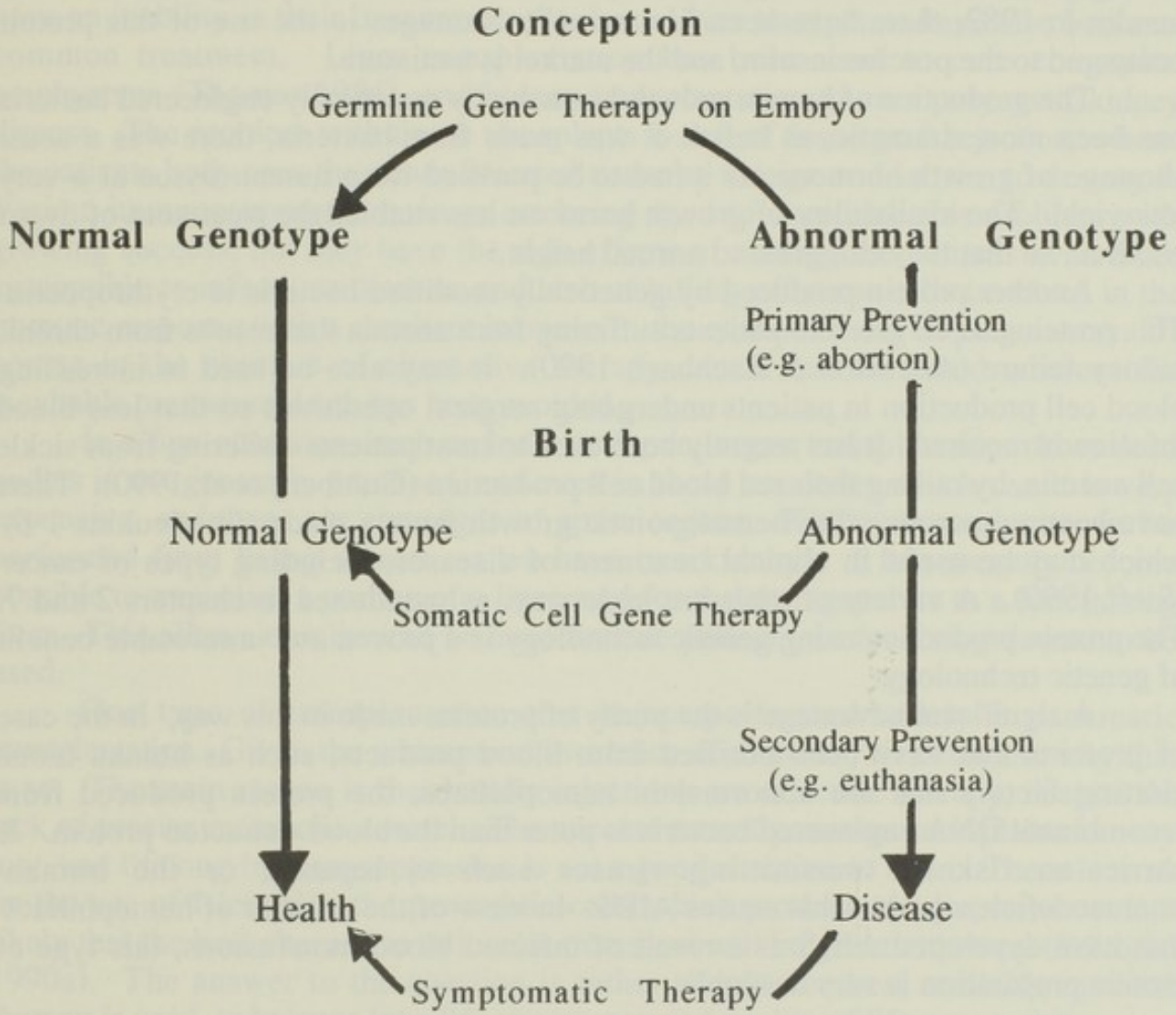
Due to recent rapid advances in molecular genetics it is now possible for the initial application of the technique of gene therapy, where the genes that are causing the defect are themselves substituted by correct genes in the patient to cure the disease. There are two levels whereby this can occur, and they differ in the consequences they have for the patient. Also, please note, the expression gene therapy has long been used, but the term genetic therapy may be clearer. The DNA can be repaired by correction of the mutation, which may only require a few base pairs of DNA within a gene to be replaced. Thus our definition for gene therapy does not mean that all the gene must be inserted, only that the repairs are effected upon genes and not proteins or other parts of metabolism.

The genes that are inserted can be put into specific cells of the body where the defect is causing the disease. This is called somatic cell gene therapy. All cells in the body have exactly the same genotype, or DNA, as they were all derived from copies of the same original fertilised egg. What makes them different, as evident in the many different types of tissues in our body performing different functions, is that they use different parts of the total genotype. So the genetic defect is often only noticed in one specific tissue, and the aim of somatic cell therapy is to insert the normal gene in a specific affected tissue. For enzymes with diffusible substrates or products, not all tissues may need to be treated. It is only necessary to treat enough cells to provide adequate amounts of the enzyme in the body, so the affected tissue itself may not even need to be treated, as long as the protein reaches its site of action.

The other class of gene therapy is called germline gene therapy. In this the gene is inserted into the germline (e.g. sperm or eggs), and hence when this individual reproduces their offspring will have this inserted gene also instead of a defective allele. It is also possible to insert a gene into the early embryo so that it will be in the germline of the new individual as well as the somatic cells. Because any gene inserted in the embryo would be heritable by future generations, most governments have limited all gene therapy experiments to only be with somatic cells. This is until the public has had sufficient time to decide if such experiments are desirable at all and on what kinds of disease. This will be considered in chapter 15. Let us first examine the alternative therapies to somatic cell gene therapy.

There are several stages in life in which medical treatment for a genetic disease can occur and these are summarised in Figure 14-1. We have discussed the use of primary prevention in the last chapter. The subject of this chapter is at the next level of the diagram. The advantage of gene therapy is that it will solve the problem. It is

Figure 14-1: Types of Treatment of Human Genetic Disease After conception the genotype may be normal, that is without a genetic disease; or abnormal, with a genetic disease. There are several stages at which therapy could occur, germline gene therapy must occur on the very early embryo. After this stage somatic cell therapy can be performed, before birth or after. Symptomatic therapy usually occurs after birth, but may also occur before birth in some diseases with modern medicine.



like fixing a hole in a bucket, rather than trying to mop up the leaking water. It represents more of an ideal therapy than secondary methods.

The knowledge of the biochemical basis of genetic disease is often essential in order to develop a reasonable therapy. In the majority of genetic diseases there is some therapy available and in some cases the therapy can effectively restore normal health in spite of the continued presence of the abnormal genotype.

Protein Replacement

Symptomatic therapy involves using the normal gene product as a substitute for the defective gene product. One of the first diseases to be treated in this way was diabetes mellitus. Diabetes is due to inadequate production of the hormone

insulin. The treatment varies from just a diet which is low in carbohydrate, to taking regular amounts of the hormone insulin to ensure a sufficient level in the body for normal function. Insulin is a relatively simple molecule so it has been produced in large amounts for some time. It can be obtained from animal tissue extraction, usually pigs, or the exact human protein can now be produced from specially genetically engineered bacteria. The bacterial production is less cheaper, but more importantly the human protein can be used rather than an animal substitutes. Though in the case of insulin, since the use of the genetically engineered human insulin in 1982, there have been few actual advantages in the use of this protein compared to the porcine insulin, and the market is a mixture.

The production of human growth hormone by genetically engineered bacteria has been more dramatic, as before it was made from bacteria, there was a acute shortage of growth hormone, as it had to be purified from human tissue at a very low yield. The availability of growth hormone has enabled the treatment of dwarf children, so that they can grow to normal height.

Another protein produced by genetically modified bacteria is erythropoetin. This protein can be given to patients suffering from anemia that results from chronic kidney failure (Adamson & Eschbach 1990). It may also be used in increasing blood cell production in patients undergoing surgical operations so that less blood infusion is required. It has recently been used to treat patients suffering from sickle cell anemia, by raising their red blood cell production (Goldberg et al. 1990). There have been numerous other hematopoietic growth factors made (interleukins 1-6) which may be useful in clinical treatment of diseases, including types of cancer (Sieff 1990). A variety of trials are underway, as mentioned in chapters 2 and 7. The protein production using genetic technology is a proven and unrefutable benefit of genetic technology.

A significant advantage is the purity of proteins made in this way. In the case of proteins that have been purified from blood products, such as human blood clotting factors that are abnormal in hemophiliacs, the protein produced from recombinant DNA engineered bacteria is purer than the blood extracted protein. It carries no risk of transmitting viruses such as hepatitis, or the human immunodeficiency virus that causes AIDS. In view of the number of hemophiliacs that have developed AIDS as a result of infected blood transfusions, this type of protein preparation is very desirable.

Dietary Treatment

Substitutional therapy is not successful in every case, as we may not be able to administer the defective gene product or enzyme from outside the body. In phenylketonuria (PKU) the defective enzyme is localised in the liver and a substitute can not be inserted. However, the disease can be successfully treated by a dietary treatment involving a reduction in the intake of phenylalanine. This is possible because the disease only affects people due to the accumulation of an abnormal toxic product derived from a specific substance in the diet, so these people can live otherwise normal lives if they omit this substance from their diet. In many countries it is compulsory to screen newborn infants at birth for such diseases, so that treatment can be employed immediately.

Tissue Transplantation

Many diseases can be treated by blood transfusion, such as thalassemia, hemophilia, congenital emphysema or leukemias. There are increasing concerns over the use of blood transfusion because of the risk of virus transmission. It is also a labourius procedure, requiring continuing visits to a hospital. A better solution is a one off treatment. For some diseases tissue transplants can be used.

Bone marrow and fetal-thymus transplantation have been used in individuals affected by rare genetic immunodeficiency diseases, disorders in which patients have an inability in their immune mechanism. Liver transplants have also become common treatment. Liver transplantation has been used to cure congenital emphysema (Thomas 1986), and kidney transplantation to cure polycystic kidney disease. The problem with tissue transplants is that of tissue graft rejection, where the patients body sees the newly inserted tissue as foreign and so tries to destroy it. Various immunosuppressive drugs are being used to overcome this problem with growing success, but they have the side effects of making the patients even more susceptible to infectious disease, and also of killing off some cells involved in the immune response with a resultant increase in the chance of developing cancer. Of course in the absence of alternative therapy cancer can be cured whereas the inevitable premature death has been avoided.

In a few countries, such as India or Japan, organ transplantation from dead bodies is not generally practised, and even in those countries which use it is very expensive, and there are shortages of spare organs. Kidney transplants can be performed from living donors, as we have two kidneys. It has recently become possible to transplant a portion of a liver, and for that to regenerate to a functioning liver. This allows one liver to be used for two patients, or for living donors to be used.

One type of transplantation that is not performed widely is pancreatic transplantation. Given the widespread incidence of diabetes, we must ask why this is so. The main reason is that insulin injections are effective therapy, despite the lack of precise metabolic control. The success rate of pancreas transplants is very low, and lifelong immunosuppresion is not a good situation to be in. There is work on the use of Islet cells, the pancreatic cells which produce insulin, however it is likely that the best alternative to insulin treatment will be genetic therapy (Editorial 1990a). The answer to the question is rather simple, the best available medical therapy is used, to balance long life expectancy and quality of life concessions.

Unlike most solid organs, the bone marrow is capable of self-renewal, and some of it may be removed without harm to the donor. Many blood disorders are the result of defective genes in bone marrow cells. The bone marrow is easy to manipulate *in vitro* and is transferred into a recipient by intravenous infusion. Bone marrow cells all arise from pluripotent stem cells, which are capable of self-renewal and at the same time, of differentiation into various cell lines. There are many factors still to be understood that contribute to cell growth and differentiation. Bone marrow transplantation has an established role in the treatment of some genetic diseases (Parkman 1986). Many patients have now been cured by the transplantation of intact marrow cells who were suffering from beta-thalassemia, ADA deficiency, glucocerebrosidase deficiency (Gaucher's disease) and some other genetic diseases..

The degree of success depends on the status of the disease at the time of transplant, but in all categories there are long-term disease-free survivors (O'Reilly

1983). More than 20,000 bone marrow transplants have now been carried out, though there is still much research needed to determine the major causes of failure (Bortin & Rimm 1986). However, even with good immunosuppressive drugs, there is the problem of tissue or cell rejection, and host-graft disease can lead to the death of 20% of patients within a year (Nichols 1988). When histocompatible donors are available and immunosuppression is used, 90% of the children with beta-thalassemia may be long-term survivors (Lucarelli et al. 1990). Despite the success rate, there are problems in finding histocompatible donors, and many patients cannot be treated (Parkman & Kohn 1990).

Somatic Cell Gene Therapy

The medical idea of gene therapy is to treat genetic disease directly by correcting gene defects in a patients' DNA, rather than the current indirect therapy using drugs or injections and transfusions of the proteins that the defective genes don't make. The strategy involves gene replacement, gene correction, or gene augmentation (Friedmann 1989). Many genetic diseases are not satisfactorily treated by current therapy, and in fact the idea of correcting the disease at the root level, the defective gene, rather than using drugs with various side effects, or transfusions with the risk of transmitting virally-transmitted diseases, is very appealing.

Diseases Suitable for Gene Therapy?

Gene therapy is generally considered to be applicable only for single gene disorders until our genetic knowledge increases. Single gene disorders do have a large impact on human health. They affect more than 1 percent of liveborn infants and account for about 10 percent of admissions to pediatric hospitals (Nichols 1988). The current treatments can only increase lifespan to normal in only about 15 percent of the disorders. It is now considered feasible for diseases in many different tissues, such as the bone marrow, liver, central nervous system, the circulatory system, and for certain types of cancer. Over one hundred human genes that have been shown to be causally related to specific genetic diseases have been already isolated (Davies & Robson 1987), so there is the potential for wide use of the technique once it becomes practically possible. It may replace many of the unsatisfactory treatments.

There was an early unsuccessful experiment in 1980 using human gene therapy, which was halted as it was judged to have been premature and also was unauthorised, by Dr. Martin Cline (Robin et al. 1987). Since then, in each new year the speculation has been that clinical use of gene therapy will begin that year. At last, after much debate and technical delays, the US Government Advisory Board judged a proposal acceptable. This was after various court cases brought by opponents.

First Approved Trial

The first approved human experiments have begun in the USA using the technique of somatic cell gene insertion. It is still very much at the experimental stage but the scientists did have to meet very strict criteria in order to conduct their experiments (Culliton 1989a), and further trials are under regulatory consideration

(Gershon 1990a). The first trial did not replace a defective gene, but inserted a marker gene into cells for tracking the cells involved in a cancer therapy.

The therapy involves the use of cells which attack cancer, called tumour-infiltrating lymphocytes (TILs). They are isolated from the patient's own tumour, then grown in large number *in vitro*. The cells are then given back to the patient, and stimulated by a naturally-occuring hormone, interleukin-2. The procedure is known to help about a half of the patients. In order to discover how this therapy works, the TILs were genetically marked to trace them in the patients. The initial trial involved ten patients, but this number has now been increased following the success of the preliminary group of patients.

The next trial will attempt to insert the gene to express the hormone, interleukin-2, themselves so it is self-sustaining and more targeted; as the first trial has been successful (Culliton 1989). A trial involving the insertion of the gene for tumour necrosis factor in TILs which will be conducted in fifty patients with advanced melanoma, passed the final stages of approval in August 1990. The trial will be led by the same researchers, Steven Rosenberg of the National Cancer Institute. It should have been easier to justify ethically because there is some hope of therapeutic value in this trial. Tumour necrosis factor has been shown to shrink tumours in mice, and it is hoped that the TILs will cluster around the tumours, releasing the factor which will kill the tumour, and then the TILs will die so that the production of the tumour necrosis factor is limited to such sites (a high blood level is toxic).

There are another two protocols under review for gene insertion for marking cells in cancer treatments that are being considered in August 1990, from different researchers. These include attempts to determine the mechanism of bone marrow reconstitution following autologous bone marrow transplantation with marked cells (using the same gene marker in TIL cells). More will follow, especially if the results continue to be good. Researchers in other parts of the world will be awaiting the results before pressing ahead with similar trials.

Enzyme Deficiencies

During the 1980's it was thought that the first patients involved in gene therapy trials would be sufferers of several rare enzyme deficiencies, all with fatal symptoms. Because many genetically determined diseases involve the bone marrow, and bone marrow transplantation techniques are effective for curing many diseases, there have been many preliminary animal gene therapy trials aimed at changing the pluripotent hematopoietic stem cells of the bone marrow, the "parental" cells from which all blood cells come (Bernstein et al. 1986, Thomas 1986).

One of these diseases is ADA (adenosine deaminase) deficiency (Caskey 1986). The lack of the enzyme ADA destroys the immune system. There are up to 50 sufferers of ADA born annually in the USA. The cells of the body which make ADA are in the bone marrow. The bone marrow is removed from the patient, and then the cells are infected with a harmless virus which has been made containing the gene for ADA. The gene then becomes part of the recipient bone marrow cells DNA along with the carrier virus. The current efficiency of gene transfer into human hemopoietic stem cells using retroviral vectors varies, up to 25% success has been obtained. However, there are problems with the continued expression of the transferred genes. After genetic modification in the laboratory the cells are placed

back in the patient using bone marrow transplantation and the cells need to continue to produce ADA, thus curing the disease and preventing certain infant death.

Up until very recently there was no alternative treatment for sufferers of ADA, a reason why experimental gene therapy methods will be used, since they will die if not treated. Some researchers feel that alternatives will be improved to work more reliably than the gene therapy, but as a longterm cure the gene therapy approach offers much wider scope. The major reason that the trials were postponed was that an alternative treatment was partially successful. In 1987 trials were set to begin, but in December of that year results of another experimental therapy of administering the enzyme, ADA, itself were successful. Using the principal principle of medical ethics, to attempt to benefit the patient using the method with the best chance of success, the trials were postponed by Dr. Anderson, the leader of the group that has been responsible for the approved trial in 1989. While, an earlier trial may have accelerated the progress of gene therapy in general, it may not have been ethical to do so. After there have been some successful gene therapy trials, this disease will be tackled using gene therapy.

The more general name for these diseases is severe combined immunodeficiency (SCID). It is extremely rare, affecting about 40 children worldwide each year. About 25 percent of those with SCID suffer from ADA deficiency. ADA degrades certain products that interfere with DNA synthesis, thus killing cells, especially the T-cells of the immune system. The most effective therapy available is complete isolation of the patient so that they are not exposed to infectious agents. Some in the press have called these unfortunate children "bubble" children, because they need to live in a sterile plastic bubble. Bone marrow transplantation can be used if a suitable donor is available. A new conventional therapy was approved in April 1990, is called PEG-ADA, and it combines the protein ADA with another molecule enabling the enzyme to survive intact longer. PEG is a nontoxic polymer. PEG-ADA is not a cure, rather it converts severe combined immunodeficiency to partial combined immunodeficiency. The patients had weekly treatments of PEG-ADA with clinical response to the drug without serious side-effects. Some have been able to go out of isolation and join their families or attend school.

In April 1990, Anderson and Blaese and a group of scientists presented their proposal for gene therapy of ADA deficiency to the Human Gene Therapy subcommittee of the U.S. National Institutes of Health. It had many committees (a total of eight layers of review) to pass through before approval, given in August 1990 for a trial of ten patients. The proposal for gene therapy was measured against this new alternative for treatment, for the interests of the patients in the trial. Even though gene therapy is the better longterm treatment, and it may represent a cure, the procedure must be assessed for the best interests of those children. The test was finally accepted by the final step in the process, the National Institutes of Health (NIH) committee in August 1990. The test entails removing T-lymphocytes from the patient and introducing the ADA gene into them. However, the lymphocytes have a limited life, so the entire procedure will need to be repeated, though they may last twenty years, much more than the current lifetime of these patients. This does represent the beginning of therapeutic somatic cell gene therapy.

ADA deficiency is a useful model for other diseases that affect the lymphoid system. ADA deficiency is heterogeneous, with patients retaining 0.1 to 5% of the

normal level of the enzyme, but this level is still too low for normal immune function. A level of 5% normal is adequate, so the expression of the gene does not need to be great (Akhurst 1990). ADA-deficient T lymphocytes have normal ADA levels following retrovirally mediated insertion of the normal ADA gene. There has been very little success in attempts to infect stem cells of the bone marrow, but lymphocytes have very long lives (greater than 20 years) so it is still very useful if they can be treated. By the time twenty years has passed they will be ready for the next round of therapy, which should be improved! The presence of the ADA gene inside cells will probably provide better detoxification than the presence of extracellular PEG-ADA. There is evidence from studies using human cells in SCID-mice that the human lymphocytes are functional (Parkman & Kohn 1990). In the gene therapy trial the patients will not require any chemotherapy.

There are sufferers from other immunodeficiency diseases which could soon be involved in gene therapy experiments (Kantoff et al. 1988). These include Lesch-Nyhan disease (a deficiency in the enzyme HPRT) and PNP deficiency. Effective retroviral vectors carrying the human HRPT and ADA have existed for a few years (Nelson et al. 1986). Lesch-Nyhan syndrome was one of the first models of gene therapy, but it has many limitations. The target organ is the brain, and most neurons are inaccessible to infection by retroviruses. It may be possible to use vectors developed from herpesvirus, which does infect neurons. It may also be possible to graft other cell types, such as genetically modified fibroblasts into the brain to act as the therapy. This type of therapy is also being researched for possible use against Parkinson's disease (Friedmann 1990b). Gene therapy is being considered in several laboratories, particularly in the USA, but there is also research in Japan and Europe.

Thalassemia is a major health problem in many parts of the world. The additional problem in this disease is that the abnormal marrow cells that make the abnormal haemoglobin, must be completely erradicated, unless the genetically corrected cells grow faster, otherwise the abnormal marrow cells will continue to produce the abnormal balance of haemoglobin and there will still be disease problems. There are patients living normally 4-5 years after bone marrow transplantation, so it is possible to treat this disease, but gene therapy is preferable. The major problem is control of the level of gene expression, more important in the production of haemoglobin, than the immunodeficiency diseases. There are many experimental therapies, including drugs which alter the DNA of cells. One drug which has been used medically to alter gene expression is 5-azacytidine (Jones 1985). This was administered to patients with sickle cell anemia and thalassemia in an attempt to correct the haemoglobin expression. In these diseases only the adult haemoglobin is defective, so by switching the expression of haemoglobin genes from adult back to fetal genes, functional haemoglobin was produced (Charache et al. 1983). The mechanism of this switch in gene expression is unknown, but it appears to alter DNA methylation (which alters control of gene expression). The ethical factors involved in using this type of therapy are similar to using somatic cell gene therapy. Because protein expression needs to be more precisely regulated in these diseases, it is further off. Though by the time that gene therapy has been tried, and the techniques tested and improved, the ability to replace genes precisely will be developed. If the possibility of treatment is better than with the alternatives, then it could be ethically tried.

Preliminary tests on the treatment of the disease PKU have begun with the expression of the protein deficient in sufferers with PKU in human and murine liver cells after infection with a recombinant virus containing the gene for correction. This is the first step towards the goal for somatic gene therapy for PKU (Ledley et al. 1986, Woo et al. 1986). One problem is that liver cells, hepatocytes, are normally resting cells, but cell division is required for integration and expression of retroviral sequences. On the positive side, the expression of 1-5% of the normal enzyme level may be sufficient to cure the disorder. Liver transplant, or grafting could be used, as it is increasingly used for surgery but gene therapy may be better as there is a shortage of livers and rejection problems. Another disease of the liver that is a target is familial hypercholestemia.

There are also delivery problems in targetting pharmacological compounds. For many proteins, especially hormones, it is desirable to release the protein continuously at a controlled rate over a period of weeks. Injectable, biodegradable polymers have been developed to give controlled release of proteins (Hutchinson & Furr 1987). For genes expressed in the liver targetting vesicles may be required, which may benefit from this technology. One possible receptor for use in targetting is the liver asialoglycoprotein receptor, which a mutant form of sendai virus uses to infect cells through (Markwell et al. 1985). Possibly altered viruses carrying the chosen genes may be able to enter hepatocytes through this receptor, and so genes could be targeted specifically to hepatocytes if injected into patients.

A more natural type of vesicle is liposomes. They consist of a lipid bilayer enclosing whatever is put inside them, in this case, the genes. The liposomes will fuse with the cell or even nuclear membrane, delivering the gene and disappearing. By putting attractive charges or targetting proteins on the surface of the liposomes they fuse more readily with target cells. This approach has worked *in vitro* for for some human glioma cell transfections, using an interferon gene (Yagi 1990). It is another approach to gene targetting under development.

Another disease is citrullinemia. Dietary and drug therapy allow for prolonged survival, but a more desirable goal is to cure the disease by the insertion of the gene for argininosuccinate synthetase into the patient. Normally this enzyme is expressed highest in the liver, but in this case, a therapeutic effect could be obtained by expression of the gene transferred successfully into human skin cells which corrects the defect. Skin cells are also possible sites for gene therapy, to cure albinism.

Multiple Gene Disorders

These diseases have a known gene cause, but are only a small proportion of the total. Current research is concentrated on single gene defects. However, most common diseases, such as cancer, are caused by multigene events (Marx 1989b), so by the time that the initial trials of gene therapy have been judged safe, our knowledge will have developed to the stage of tackling a broader spectrum of diseases. By the time the technology of gene therapy has been used and improved many more genes will be known and thus diseases treatable. Within the next two or three decades the entire human genome will be sequenced, and potentially all will be treatable. The ethical question will have moved from safety to the desirability of treating all genes. Many genetic diseases are caused by complex traits, multiple genes, and it is not thought that these would be able to be treated by insertion of

single genes. Though in some cases insertion, or replacement of single genes will have some worthwhile affect, but currently the affects are unknown. Some single gene disorders are caused by dominant traits, these may be treatable if the damaging gene can be deleted and possibly replaced by the normal allele.

The progress in gene targetting in the last five years has increased the possibility for precise gene repair, and by the time that these diseases are understood, such repair should be possible. Gene therapy is now considered feasible for diseases in many different tissues, such as bone marrow, liver, central nervous system, the circulatory system, and for certain types of cancer (Friedmann 1989).

In August 1990 a gene therapy trial was approved to treat a type of cancer. The gene for tumour necrosis factor, a protein that kills cancerous cells, will be inserted into TILs, as described above. This is indirect therapy. It will be possible to use directed genetic screening and therapy to detect and prevent some cancers. Cancer is a very broad term for many diseases. About 2% are directly inherited disorders, such as familial polyposis. This type of disease suggests a single dominant mutation is responsible (Ponder 1990). There are also many cancers which appear in familial clusters, such as breast and ovarian cancer. The degree of risk in the family may be 2-3 times higher than the general population. Genetic diagnosis is feasible, so that regular screening for cancer can be given to those at high risk. With the development of gene therapy, the risk groups may be treated so that they are no longer at high risk for these conditions.

In the future it may be possible to insert genes from harmful viruses into our cells for immunization. The products of such genes would not be harmful, but would prevent the effects of harmful viruses in a type of intracellular immunization (Baltimore 1988). It is suggested that it may work with AIDS virus, but it is more speculative than the other uses of gene therapy discussed. It would only be used with infected patients, time will tell if it can work.

Fetal Gene Therapy

Another major purpose of somatic cell gene therapy will be during fetal life, as many diseases require treatment to begin during fetal life (Robertson 1985). The alternative is selective abortion, at an early stage. The future situation, as we considered last chapter, may make early fetal screening routine, by chorionic villi sampling at 6-8 weeks, allowing the screening of any genetic disease. If a disease is detected then the decision will be whether to to have a selective abortion, and have another fetus, or try to treat the disease. As the number of gene probes increases it is possible that all the embryos will be shown to carry the 5-10 harmful recessive alleles that they contain, and one could imagine the situation where it is very hard to find a fetus free of a potentially harmful allele, or that will not have a risky allele and the tendency for some disease, so therapy will eventually dominate.

Fetal surgery or therapy or dietary supplements have been used for many diseases already, and the increasing use of conventional therapy will be supplemented by gene therapy. If there is a risk of harm to the fetus then it may be more ethical to use selective abortion at that early stage. It is seen by many that it is more ethical to end the life of a presentient human embryo than to let the embryo grow to become a person, or to try experimental therapy on the embryo and risk the damage to the child. The question of selective abortion comes down to the status of

the human embryo, and the possibilities of earlier screening. The technology is here, and already some parents have had to make these type of decisions, we all need to examine our response. The choice will depend on the type of disease.

The situation will be reached where if a disease is diagnosed that requires treatment, it will either be abortion or therapy, it will be unethical for parents to knowingly fail to treat their fetus or children that are sick. There will be major ramifications of the new technology, and it will change the way that we reproduce. There will be some objections from people who do not want this treatment imposed on what they see as their property. We need to be responsible for our children, and that includes the time that they are still in the womb. Does this mean that we should not overdrink or smoke or take harmful drugs during pregnancy? In my opinion, yes, we do not have the right to do whatever you like, but rather that we should be responsible to the poor, the sick, and weak, and heal them. Almost all parents want the best for their children, and should seek medical help. Rather than being full of fear, we should welcome the ability to treat more of the diseases, and alleviate more of the suffering that they cause.

Results of Animal Gene Therapy

There have been experiments on animal models as a prerequisite to experiments on humans. There have been several animal systems for testing human gene therapy made. Retroviruses have been successfully used to target genes into animal cells for several years (Thomas 1986) and foreign genes have been expressed in mice, using treated cells (Bernstein et al 1986, Keller & Wagner 1986). Larger animal models are under study to determine the persistence of infected bone marrow cells in transplanted animals (Anderson et al. 1986, Kwok et al. 1986). Various types of retrovirus vectors have been developed. Human bone marrow cells have been infected and expressed inserted drug-resistance genes (Miller et al. 1986). There was expression of the human ADA gene in murine cells in vivo (Williams et al. 1986). One group of scientists placed the human gene for the production of ADA into the bone marrow of Rhesus and Macaque monkeys and fetal sheep in preliminary experiments (Anderson et al. 1986). Several experiments using SCID-mice and human ADA-deficient lymphocytes expressing an inserted ADA gene have been successful, as described. Other groups continue to work on procedures to infect hematopoietic stem cells, for diseases such as ADA deficiency (Cournoyer et al. 1990). These are the reason for optimism with the approved gene therapy trial, it is based on years of preliminary work by many groups. The human globin gene has been expressed in mice that were treated with retrovirus infected stem cells, so the expression problem in stem cells may be soon overcome (Dzierzak et al. 1988).

Another experiment performed in mice was to test a model for treating retinoblastoma In tumour development both positive acting oncogenes needed to be switched on, and negative acting tumour suppressor genes need to be mutated. Both alleles of the suppressor gene need to be turned off before cancer can proceed. In gene transfer studies the suppressor gene function for retinoblastoma could be reinserted and tumour cell formation repressed preventing the tumour formation (Freidmann 1990b). This work may be extended to humans.

There is a contrast between diseases that affect the lymphoid cells and

diseases that affect the hematopoietic system. The hematopoietic cells have a short life so they cannot be useful targets of gene therapy. One of these diseases is Gaucher's disease. Human cells have expressed the gene for glucocerebrosidases needed for correction of Gaucher's disease (Choudary et al. 1986, Sorge et al. 1986). It is another disease with no known cure, which affects 0.2% of people born (2% of Jewish population). The absence of glucocerebrosidase results in the accumulation of non-degraded membrane lipoproteins within the reticuloendothelial cells. An appropriate *in vivo* model for the detection and measurement of pluripotent hematopoietic stem cells does not yet exist. Further experiments are needed, but there is some progress (Parkman & Kohn 1990).

The virus must not only be efficient for transferring and expressing the transduced gene, but it must also be safe. It is possible that the retroviral vectors might activate endogenous retroviral genomes in target cells by recombining with them and expression of the genes inserted has proved difficult. The use of disabled viruses is probably essential to "ensure" safety. The study of gene expression is also essential, it has been found the retroviral vector used to transfer genes into cells does alter the expression of the inserted gene. The chromosomal sites which retroviruses integrate may be fundamentally different from sites into which DNA segments integrate using DNA transfection without a viral vector.

Some problems have been eliminated, and others will be as further trials are undertaken. One of the positive outcomes of extensive animal trials has been the development of effective and stable retroviral vectors for gene transfer. There are alternatives to retroviral vectors being developed, such as methods of targetted modification of human genes (Gregg & Smithies 1986, Thomas & Capecchi 1986, Capecchi 1989), and these will soon be possible. Promising alternatives to retroviral vectors are being developed, such as the use of laser micropuncture of the cell membrane to facilitate direct gene transfer. This technique has been used on cultured human cells with an efficiency 100-fold more than the standard calcium phosphate mediated method of DNA transfer in which cells are passively incubated in the DNA solution (Tao et al. 1987). There are also new techniques for electroporation, and microinjection, and even high velocity tungsten microprojectiles containing DNA. The efficiency of the physical methods is about 1% of the target cells incorporate the genes (Friedmann 1989).

If there are no naturally occuring animal models for some human genetic diseases, targeted gene mutagenesis can be use to create diseased animals. Mice have been genetically engineered using embryonic stem cells to be HPRT-deficient mice. These were hoped to provide mouse equivalents of Lesch-Nyhan disease suffering humans. Genetic therapy has been tried on them, as preliminary experiments for human gene therapy (Friedmann 1987), correcting the gene deficiency. However, in this case the HPRT-deficiency in mice has been found not to result in a disease such as human Lesch-Nyhan syndrome, so it is not a full model at the animal level, only at a level of restoring gene function. It is still useful for studying gene function, though some people disagree with the creation of diseased strains of animals (Macer 1989).

There have been a variety of trials in animals. There is some progress on gene transfer methods. Lipoprotein vesicles using the substance lipofectin have been used to insert genes into the neuroepithelium of frog embryos, as well as into skeletal muscle cells of young mice. The biolistics approach used in plants for gene

transfer is being applied to animals, and will also be used in the gene therapy trial on ADA gene insertions in humans that has been approved. The gun shoots DNA-coated gold microprojectiles, using high pressure gas, instead of the gunpowder used in plants. It has been used for different animal tissues with some success, and will be useful.

In a recent report, work on heart disease was reported. Heart disease afflicts millions of people, so is much more numerically significant than ADA deficiency. Rabbits of a strain called Watanabe lack the receptors for low-density lipoprotein (LDL), cholesterol. This means that they cannot remove the bad type of cholesterol from their blood, so they develop atherosclerosis. A team of researchers led by Wilson and Mulligan, took the rabbits liver cells out, and inserted the gene for this receptor, and implanted into the rabbits. For two weeks the genes worked, although they only expressed about 4% of the normal activity of LDL receptors, the blood level of LDLs dropped 35% (Marx 1990). However, for some reason, yet unknown, the genes did not work for longterm. This type of gene transfer experiment is becoming very common, and within this decade we can expect more therapeutic use of somatic cell gene transfer.

Inserting Organoids

There are important limitations on the use of specific tissues, such as bone marrow cells. An alternative approach to removing, altering and replacing bone marrow (or most other specific tissue cells) is to remove and transfect cells from a chosen source in the affected individual. This involves isolating a suitable cell from the patient (to avoid immune rejection upon subsequent insertion). After genetic manipulation in vitro, chosen cells are cloned (grown to increase the number of identical cells), than tested to check if there is proper regulation of the transfected gene, and then these cells are reintroduced. Of course many tissues are impossible to replace.

In a preliminary test, a gene was transferred into cultured mouse fibroblasts and subsequently these cells were implanted into various locations in mice (Selden et al. 1987). It was found the function of implanted cells depended on the location and size of implant. The technique is called transkaryotic implantation, and it is a promising extension to the range of possible gene therapy techniques. The efficiency of gene transfer into different cells varies, and it is highly efficient into human fibroblasts, 87% efficiency is already obtained (Miller et al. 1986).

Hemophilia B is a disease caused by a lack of blood clotting factor IX, affecting 1 in 30,000 males. Current therapy involves injection of the protein. The protein is normally made in liver hepatocytes, but recently the gene has been transferred by retrovirus, and expressed in a fully active form in human skin fibroblasts. This may allow the use of skin grafts for gene therapy of hemophilia B (Anson et al. 1987). Human skin cells from patients with ADA deficiency have been infected with the ADA gene in a retrovirus and have expressed the gene, making the enzyme ADA (Palmer et al. 1987). The next step is grafting the treated skin cells back into the donor to see if the level of expression of ADA is sufficient to cure the disease.

Many disease treatments do not require the production of the corrective protein at a specific site. For blood protein disorders it would be possible to insert a cluster of cells making the required protein at any site where blood vessels could

deliver the protein to the rest of the body. Because skin cells are easier to graft, they may be used, or fibroblasts could be inserted into other solid tissues. Because bone marrow stem cells are more difficult to correct, this alternative delivery system may be chosen.

Researchers have recently created an artificial organ, or organoid. The first such organoid was an artificial liver which was implanted into the peritoneal cavity of a rat. It was made using an artificial fibre, "Gore-Tex", and cells. The trial involved using cells that produce Heparin-binding growth factor 1, a factor that induces the development of blood vessels (Thompson et al. 1989b). There needs to be cells to generate blood vessels to flow through the organoid, and cells to produce the protein, or other product. The first use may be to produce a protein, CD4, which helps slow down the development of AIDS (Culliton 1989b). There are many potential uses for this approach in medicine, and it should result in rapid progress.

There are certain organs which may be very difficult to use somatic cell therapy on. If the gene is required intracellularly, and inside a particular organ, germline gene therapy may be the only way. However, tissues such as muscle and the brain, which are nondividing cells and were thought to be very difficult for somatic cell therapy, are now being investigated as serious research. Once tissue targetting vectors have been developed, then they should be possible. One approach is to use other cells to associate with these organs and transmit diffusable gene products to the cells that need it.

Ethics of Somatic Cell Gene Therapy

Those people who support the use of gene therapy stress the teological principles that genetic disease causes suffering, both pain to the individuals suffering and their being a burden on others. Medicine is right to try to cure disease and alleviate suffering. Gene therapy is a new form of medicine and if properly controlled it will lead to the sufferers' being able to live healthier and fuller human lives, which can lead to a higher quality of life. Biologists may feel that the very nature of DNA and ease of manipulation to cure disease makes it an obligation of stewardship, not just of greater good. The opponents have reservations as they feel that gene therapy is unusual and untried, and wonder if there has been enough experimentation to warrant use of such techniques on humans (Friedmann 1983, Anderson 1984, Culliton 1985, Robertson 1986, Walters 1986, Nichols 1988). It may lead to the abuse of genetic control and to decreasing human value. And the legalists ask who has responsibility for unforseen problems.

The deontological argument applies to the patients, and to whether their rights are being removed and whether man should be altered genetically. God is concerned with every individual human in creation, but while we are all given a unique genotype, the defects caused by mutations are treated in medicine and there is nothing inherently evil in altering the genotype to cure disease. First we will examine the government guidelines that apply to gene therapy, and the factors that they concentrate on.

Government Guidelines

The situation regarding the major ethical debate over gene therapy before its use, is in major contrast to the situations with the use of other new reproductive and genetic techniques, such as genetic screening, selective abortion, embryo experimentation and IVF. With a few exceptions, these other techniques were discussed in greater depth after they were technically possible, and while they were being clinically used. However, there have been ethical guidelines preventing human gene therapy for the last decade in the United States, since the first use of gene therapy in 1980. The European Medical Council (1988) has also recently made a statement on gene therapy. There have been statements from other countries, such as Australia, and there is currently a committee examining guidelines appropriate for Britain.

The procedures that have been decided upon in the USA for researchers to obtain US government approval for gene therapy experiments upon humans are quite elaborate (RAC 1986). The researcher must answer the following questions.

Why is the given disease a good candidate for gene therapy?
Will the therapy cure the disease or merely halt its progress?
What alternative therapies exist, and how effective are they?
Technical details of the DNA and vector to be used.
What makes the scientists sure that the new gene will be properly inserted and regulated so as to be expressed usefully in the patient?
Has a similar experiment been conducted on nonhuman primates?

The major reasons that human gene therapy has been long delayed are technical delays, the risks to the patients of experimental therapy, and the fear of human genetic engineering. The government guidelines consider all of these factors. Of most importance is the regulations are the technical factors, and protecting the patients from unethical experimentation. There have been problems with the development of techniques that has delayed the date of the clinical experimental use, but overall the progress has been rapid since the first experiments with genetic manipulation of bacteria in 1974. The major technical problems can be divided into three areas (Anderson & Fletcher 1980, Culliton 1985, Walters 1986); the delivery system, the gene expression, and safety. These are important for ethical consideration of the techniques as they apply to individual patients.

The assessment process begins with an evaluation of the genetic disease to be treated. The diseases that will be the target of the first human trials are considered so devastating that experimentation in patients may be justified ethically as long as some animal data are in hand. In the case of terminal cancer patients, there is also the argument that patients should be able to consent to experimental therapy, so that they feel useful, even if the chances are very low. However, in order to protect patients from possible abuse, this is not usually sufficient justification for experimental therapy. Gene therapy has not been tested so will often be the last resort, after all other alternatives have been considered, and if the transition from animal to human studies is considered appropriate. The trial must be of potential benefit to the patient, and should be designed so that useful information will also be obtained to aid in the design of future trials.

The first approved clinical trial for human gene insertion was approved only after being reviewed fifteen times by eight different committees (Anderson 1990). This is more than any other clinical treatment. One must say that this is a case of

extreme regulation, why so many different ethical committees. We can hope that the regulators will change the procedure, as after we examine the ethical issues we will see that there is little to distinguish this treatment from other types of experimental therapy.

At the end of 1989 there was a committee established in the U.K. to look at the issues of gene therapy. It is chaired by Sir Cecil Clothier and its purpose is "to examine the implications of the prospect of treating certain conditions by gene therapy". They are to draw up ethical guidance for doctors who wish to use these techniques, and give guidance to any who want to perform such therapy (IME 1990).

Efficacy of Treatment

The new gene must be correctly put into the target cells, and remain there long enough to be effective. It would be an advantage if the cells to be directly exposed to the virus were outside the body in case something unforeseen did occur. The major problem of the viruses being used is that they can rearrange their structures once incorporated into the patient's DNA, and they may then form new viruses. But the latest designed viruses seem to be stable enough for use without likelihood of this occuring. Still studies in human bone marrow tissue cultures and studies on the incorporation of genes into mice and primates are needed, to see if infectious viruses or malignant cells can be detected, before patient trials begin. There are also alternative delivery systems that need testing.

The new gene must be expressed in the cell at the appropriate level, and only in that tissue. With ADA deficiency the proper control of gene expression is not critical because the production of any of the enzyme would be beneficial. But with diseases where many genes are defective and the products of the genes circulating in the blood stream have to be at a fixed critical concentration, simply inserting the gene is not enough as the control mechanisms may not work normally. It is safer and easier to treat these diseases by injecting precise amounts of the hormone or enzyme into the patient.

Safety of Transferred Genes

The new gene must not harm the cell or the patient as a whole. However, unlike most other medical treatments, the introduction of a virus could possibly threaten other people. The risks to the patient themselves are no higher than many other experimental therapies. This is a contentious issue because the stability of the genetic arrangement is difficult to predict. Possibly many years after treatment some environmental could trigger an unforseen event. It is however unlikely that an infectious mutant virus would be formed if the delivery system was sufficiently stable. It has recently been observed that some retrovirus vectors recombine inside the cells at frequencies of 1 in 10,000, producing wild type infectious viruses. These virus particles probably stay within the individual so are not an outside threat, but they are a potential safety concern. The fear of a contagious virus, which even in its' worst scenario might be spread like HIV, that is by serum contract only. On the basis of the limited animal experiments done, this does not appear to be a risk.

However, gene therapy is only a new technique for the treatment of disease so it should be considered in the same light as other treatments. It strikes a deeper

response because it involves changing our biological foundation which has only been altered in the past by drugs. It actually seems a better and potentially safer treatment for individual patients, since it would avoid the many side effects caused by dangerous drugs. We will also avoid problems to the patient, such as negative side effects, of conventional treatments. Potentially, gene therapy may lead to greater unforseen problems than alternative treatments because it is directly altering DNA, but in the long term it should be much safer.

For the gene therapy to remain in the class of 'somatic' therapy, affecting only the patients body cells, the gene should not be incorporated into the germline cells. The gene or viral vector should stay in the initial target tissue, if it may harm the patient being elsewhere. The risk of genetically altering the germline is not unique to gene therapy, as several other medical practices, such as vaccination, cancer chemotherapy and radiation therapy also carry this risk. The idea of germline gene therapy is more objected to, as it would after future generations. However, to most patients with the likelihood of being treated soon by such a therapy, their life expectancy being under 25 years, and who may only expect to have less than a year to live, the thought of this being a barrier to a possible treatment is far from their mind.

Some feel that genetic manipulation differs in principle from other therapeutic techniques. However, it should be judged in a similar way to any other technique. Altering the expression of genes by drugs so that some of these drugs may cause secondary changes in the genes themselves, is effectively the same as altering the patient's genotype by inserting new genes directly.

Experimentation and Protecting Human Life

The major safety concern seems to be the same as with other treatments, despite the fears of a potential viral epidemic, the safety to the patient, that is do no harm. As clinical experience is gathered it may be justified to use somatic cell gene therapy as a prefered treatment in many disorders that may have alternatives. The sole determinant on choice of treatment should be what is in the best interests of the individual patient, assuming no one else is at risk. The safety argument would be the major reason not to try germline gene therapy at present, as we do not know enough about the possible side-effects on the individual patient's or the long term risks of some sort of viral epidemic. We need to know much more about gene regulation and developmental changes before it would be ethical to try this.

Almost every action taken by the doctor in the process of relief of suffering is experimentation, as people vary in their response. No one type of diagnostic procedure or treatment may have been proved to be superior to all others in the management of a particular disease. When the patient stands to gain from investigations performed some risks are acceptable when weighed against the likely rewards. The difficulties arising from the use of technological advances are often temporary ones resulting from a lack of expertise. Common sense is required in the decision when to use these techniques. But if the patient will receive no personal advantage and is merely contributing to the welfare of future patients, any significant risk is only permissible provided the subject can appreciate the hazards and give his consent without coercion. There are obvious moral considerations involved in the choosing of a particular procedure on behalf of an individual who may be too young or mentally incapable of making a decision. Any experimentation should be in the

best interests of the patient, and a basic rule is to "do no harm". From the principle of double effect the genetic manipulation to treat disease is morally justified.

The Recombinant Advisory Board (RAC) in the USA has been asked by the Boston-based "Committee for Responsible Genetics", to ban for the indefinite future any tests of gene therapy not aimed solely at the relief of a life-threatening or severely disabling conditions. The measure of risks to be accepted in proceeding with genetic treatment is the balance of the seriousness of the illness to be relieved against the possible dehabilitating outcomes of the treatment itself. To proceed against Tay-Sach's Disease or ADA deficiency, for which there is no known cure, yes; but against cystic fibrosis, for which there is some relief, there is less certainty. To proceed to gene therapy in the case of diabetes would be an immoral trial until the technology is proven. The aim of medicine is to make a patient well or at least less ill than before.

Where there is an established treatment to cure the disease that treatment should be used. If however, compared to another technique it is more likely to be a successful therapy for that individual, the one best suited should be used. Some predict bone marrow transplantation will be used more than gene therapy, at least in this next decade, as the immunosuppressive drugs being used are good. Gene therapy may be used only when it is judged by the physicians to be in the best interests of each patient.

The patients that are current candidates for gene therapy are all suffering from a fatal disease, normally a genetic disease, but in the case of the most recently suggested trials suffering from major cancer. The first test will not require the expression of the gene, but merely the insertion of it as a marker for immune cells that attack tumours. The cells will be treated with a natural substance, interleukin-2, which aids the cells attack on the tumour. It has not been possible to trace these cells to see how they attack the disease, so a marker gene may be useful. If this works, they may insert the active gene for interleukin-2 into these cells, which my aid their activity. This possible second trial might be easier to judge ethical, as it will include the possibility of benefit to the patients. One of the genetic diseases, ADA deficiency, previously thought to be a good candidate for gene therapy trials (Kantoff et al. 1988), now has an alternative treatment which is currently being tried which has lessened the current case for using gene therapy.

One of the researchers behind these cancer patient trials, W. French Anderson, of the National Institute of Health, U.S.A., has written extensively on the ethics of gene therapy, which one could say has been a good example of a scientist thinking of the ethics of using techniques they are trying to develop, and raising these issues for public discussion. Much of the responsibility (and thus accountibility) for the use of gene therapy lies with those involved in medical practise and research. The possible side effects may not be imagined by the medical practitioners, so more responsibility rests with the researchers. Our knowledge should be used creatively, but it must at all times be used responsibly, too.

The ethics of using a experimental medical technique are well discussed, and the use of gene therapy should come under the same examination, such as the guide lines of experimental medicine on human subjects. We should not do harm, but we may undertake an "experiment" on a patient if there is a reasonable chance of therapy, and informed consent, and taking into account the life expectancy and quality of life, without this therapy. As an exercise, can you think of what

percentage of success of recovery you would consent to as worth the risk if you had three months life expectancy at the age of 20 years having spent most of your life in hospital. This is using the old maxim, would you use it on yourself?

The delays in the introduction of trials using gene therapy have partly been due to a consideration of patient rights. There has been some caution, correctly, used to protect patients from merely being "guinea pigs" when the therapy has not been previously shown to work in animals. It is not possible to regulate the use of genetic engineering by consent alone, as inadequate knowledge may be available. Parental proxy is often necessary. Poverty may lead patients to research hospitals, rather than to hospitals which use expensive alternative therapies. We must be careful in the use of new technology. However, many patients, or their families, have been frustrated by the delays over what they see as their only hope. Sometimes the media has falsely raised the hopes of the public, so that their optimism is not based on fact, but there still could be a case that the regulatory bodies have been over cautious.

Many of the diseases that gene therapy will be used on afflict children. There are special problems associated with medical experimentation on children, in the way consent is gathered. There are existing medical agreements to cover this, such as the Helsinki declaration. These allow for experimentation when it is in the best interests of the child, in light of alternatives. The research will involve children if it is their only hope. This will provide further challenges to the decision making of medical ethics.

Alleviation of Suffering

When we see suffering, or feel it, it is the more immediate solutions which are more important than the future sometimes seemingly fantastical conjectures about its longterm misuse. This is a fundamental principle of bioethics, and is called beneficience. It is important to realise that it is unethical to misuse it, but equally unethical to delay the use of techniques which are medically safe. There will be an urgent desire to treat patients that are close to death with promising but untested experiments. In many respects the use of somatic cell gene therapy may give rise to no new ethical problems compared to other treatments, but we will need to have a healthy respect for the degree of ignorance of the possible side effects of the techniques.

Already we have existing medical values to decide who is responsible when deciding treatment. There is always a danger in the unknown, the realisation of which is a good thing, but we must decide if we are objecting to something because it is wrong or because it is not "normal". In some ways all medical treatments are unnatural, but they are beneficial in that they aid the natural course of human life. The development of these technologies will involve experimentation upon future children. While we shall not kill, the primary motive in any treatment is compassion, and there is certainly no murderous intent. We will expose children to additional risks they would not otherwise be exposed to, but we will also be offering them possible life they would not possibly have. To delay beyond the point of reasonable prudence means that an undetermined number of patients will die, not only those individuals who would directly benefit, but also those in the future that could be saved if the techniques had been developed earlier.

Affect on Family Life

We may ask whether somatic cell gene therapy techniques will affect the nature of our family life. It will only affect a few people, and one would generally imagine that healthier people will be at least as good and usually better than sick. The ability to cure disease will not necessarily lead to the situation where parents will only accept a healthy child, though with the advances in medical care during this century generally people now expect to be cured. Gene therapy will certainly not erradicate genetic disease. Children may have psychological problems in knowing they are "corrected", but already therapy is performed on many. A serious concern are any physical safety problems during the development of the techniques. However, without treatment they would be dead, so this is no real problem! One future risk some see is that some parents may decide to chose their children's characteristics by genetic manipulation, which may have the affect of encouraging the replacement of personal and permanent relationships characteristic of a family with instrumental and impermanent relationships, but this should not be confused with somatic cell gene therapy in the case of diseases. Once an individual exists, human relationships are critical. Human concerns are more important than abstract speculations.

Economic Factors

The economic factors are important to consider as we use our limited medical budgets. Some ask whether we should spend our health resources in this way rather than on other areas of medicine. It may cost US$ 100,000 dollars for one year costs for cardiac transplantation (Walters 1986), so medical costs currently accepted as justified for medical treatments in developed countries are already very high. Some would say too high. With the high cost of lifetime treatment of sufferers of genetic disease (which is not possible in some countries), once a therapy is developed it would be cheaper to treat the patients only once so that then they could be working individuals in society and would not depend on hospitalisation. The argument could be extended to using germline gene therapy since it would be cheaper than somatic cell therapy, though other factors may be considered more overriding. Once a person exists, that individual is to be treated as of utmost importance, regardless of any deleterious genes they carry, or of the cost to society.

There is a more fundamental question of what proportion of health funding should be spent on research versus clinical practise. If we converted the results of research into clinically useful results there would be more shortterm advances, but longterm progress would slow. There is much research in gene therapy techniques in the USA, and in 1990 several trials have been approved. At last it may get to the clinical stage. The longterm projection means that this therapy is economically feasible. Given that the developed countries maintain that they are entitled to using high cost medicine while people in the developing countries can not afford basic costs such as vaccination programs, gene therapy is justified. It may be more justified than many other expensive therapies because of the longterm effect of reducing costs. It will be many years before people in the developing countries can use such a technique, and it is therefore not a priority of WHO nor should it be. However, in developed countries it is economically justified. Not only will the

economic costs be reduced but the cost in reducing suffering will also be on the positive side, something that not all new medicine can claim.

Public Attitudes and Fears of Genetic Engineering

The name "gene" therapy is a suitable one from the point of view of the technique, but it has raised many unnecessary fears in many peoples minds. The picture conjured up, thanks in part to some creative writers and confusion with germline gene therapy, is that gene therapy will mean genetic engineering of the human race. However, this is not what somatic cell gene therapy will do, as it only concerns individuals who are to be treated, as they have been for milleniums by medicine. The effects of some modern drugs leave more to be worried about. Some cause major damage to the patients DNA have been used (Charache et al. 1983), and many prescribed drugs alter patients behaviour markedly which may give more cause for fear or more potential for misuse. The techniques for selective abortion have greater affect on the population gene pool than any other medical treatment.

In an apt term, Gaylin has described the fear of genetic technology by the term *"Frankenstein Factor"* (Gaylin 1990). Part of this is common to all high technology research that may be unknown to the public. The fear of the unknown, is a factor in people's fear of genetic engineering. This can be diminished by good public education, which should be a lesson applied in many areas of science. The second part is that we are changing the very nature of ourselves, or at least that is how it may be perceived. While we do this by our diet, environment and other forms of medicine, for some reason the genes seem more fundamental. The ironic thing is that our culture and social system change our very personalities, what is the distinctive part of a human being or person, in greater ways than altering a few genes. This attitude may take more than education to change, but at least education of the place of genetic therapy among the many other aspects of changing our life, would help. Some caution is of course useful also.

What may occur in the future is a shift in public opinion towards a pressure upon all parents to undergo such a type of treatment once it has become routine. However, if it is beneficial, than few parents would object to it. We can see the differences between what technological societies and third world countries regard as a need today, public standards do change. It will be necessary to widely educate people about the new techniques as misinformation, old wives' tales and general ignorance have already led to some popular misconceptions. While some feel that the idea of genetic therapy is unnatural there will be a shift in opinion when it becomes routine, and it is understood for what it is, not fears of beyond that could be associated with excesses of most human endeavours. Nevertheless some people may still view it as unethical, and while they do so there may be doubts as to whether it should become enforced routine treatment. Perhaps once it has reached a certain stage of reliability it may be seen by most as a necessary part of health care. This may only be a few years away, though is a problem currently faced with some medical techniques by those people who feel the body should not be treated by transplants - maybe since it would be their own body tissue being treated it would be less of a disruption of their moral values. The judgement of use of the treatment will fall on the physicians, as with other medical techniques, but this should only be used when medically necessary, as are current therapies.

The slippery slope arguments that because we do some act, we will do another, are not always logical. If we do gene therapy to treat disease it does not mean that we will use gene manipulation to alter behaviour, morality, or appearances. They are two very separate questions, and there is a moral gulf between them. Every technology has a slippery slope, along which we decide to stop. Growth hormone replacement therapy for dwarfs allows them to become normal height, but it is objected to if suggested to make normal people very tall for certain sports. Another more difficult problem will be the use of memory-improving drugs, which while being developed to help below average intelligence children learn normally, could also be applied to normal children to help them.

Man will have the power to shape his own biological destiny. Such power can be used wisely or unwisely, for the betterment or the detriment of man. There are many issues raised by the possibility of shaping the genetic constitution of the human race, but perhaps if we are concerned about the maximal fulfilment of the potential of our fellow human beings than this could be of more benefit than potential harm. While humans do have a limited rationality, we may not always be able to discern which qualities are desirable; though we can often see ones which are not, such as disease.

When We Should Use Gene Therapy?

The goal of biomedical research has always been to alleviate human suffering, and as we have seen gene therapy is a proper part of that. The techniques are necessary and they provide new approaches. What remains undecided is whether they are ethically and socially acceptable. Just because a new technology becomes available it is not necessarily the most rational course to use it. Even if human society all agreed on a rational action, we are still sinful and so incapable of always making perfect decisions. Gene therapy has been described as a preventative therapy, preventing disease at the fundamental level. We should not forget that there are other causes of disease, and poor health, such as good diet, and health education, which are also root causes to be focused on.

Because of the doubts about success, the immediate prospect of gene therapy is limited to life-threatening diseases that do not have any other cure, and are due to a single gene defect whose effects can be corrected by the insertion of the normal gene into the bone marrow without the need for precise regulation of gene expression. Diseases of the gut and skin are similar in that like bone marrow these tissues have dividing stem cells in adults, so they may also be treatable. Since there may be no alternative treatment these new methods are necessary if we wish to treat these conditions, and they promise new approaches to disease treatment. The major disadvantage of gene therapy is the technical difficulty of expression and appropriate regulation of new genes in somatic cells. The main advantage is the compatibility of the reintroduced cells with the patient and the avoidance of immune rejection. Many patients with genetic disease do not have suitable donors for transplantation.

Gene therapy also offers the possibility of introducing novel genetic elements that, for example, may confer drug resistance to normal bone marrow cells to allow their survival during chemotherapeutic treatment for cancer. Gene therapy is another medical tool to help individuals overcome an illness, and somatic cell therapy has basically no new ethical problems from existing treatments.

What is essential is full public review of the results, which will have to be

debated much before the techniques become of wider use. While this is not required for most medical treatments, there has been so much publicity associated with gene therapy, that the results and comparisons to alternatives, should be made available to allay public anxiety. The patients, or their guardians must be educated so as to be able to decide if they will submit to the experiments, which will have to include longterm followup studies of patient progress.

The point at which we stop using gene therapy is discussed in the next chapter. It is when it no longer is a treatment for a disease, but becomes enhancement. This problem is not only when we use genetic therapy, but is also found in common practise, such as cosmetic surgery, or in the more serious case, on deciding the limits of growth hormone replacement therapy. When therapy no longer adds to human dignity we should stop using it, the same as other applications.

We must be clear that a pursuit for our lives to be free of physical suffering is not going to make the ideal world. Genetic defects have a smaller effect on people than the moral, spiritual defects and lack of love. The goal of healing is to benefit the patient - the actual patients are the "ends" rather than the "means". In this case individuals are more important than hypothetical individuals (ones as of yet unconceived), or the human species in general. Using gene therapy to improve the health for our children is not really going to trade away a part of our humanity that is worth preserving. Love can be shown in many other ways than through sympathy to people suffering from genetic disease, and may be shown more by the cured patients.

15. Human Genetic Engineering

Of the many fears over the future abuse of science, the most sensitive area is the changes that affect the inner constitution of humans. There has been much written considering the fears of human genetic engineering, and it still arouses strong passions. The technical ability has developed to a point where certain types of "genetic engineering" are possible, which makes the topic no longer one of mere speculation, but one of immediate importance in health law and ethics.

The term "genetic engineering" has caught the public imagination in a negative way, and by using it there will be a biased view. I use it in preference to another biased term, genetic manipulation. Genetic engineering is the most applicable word to the topic of this chapter, so I will use it, as I also previously used the word eugenics. The question of eugenics was central to chapter 6, but this chapter will consider more positive eugenics. A common association with genetic engineering is what people call "the Frankenstein thing" (Rollin 1986). Many people have a strong reaction to the talk of genetics whether it be on animals or talked of in humans. A major part of this response, that something is unnatural or unusual or extraordinary is not a genuine moral issue. What is the most important moral issue, whether it be regarding animals or humans, and the theme of the original Frankenstein story, is the plight of the being who is altered. This should be seen throughout the techniques.

There are arguments that are commonly used in support or against genetic engineering. In favour of genetic engineering is utilitarian thinking. Although there will be risks for individuals the goal of the application of these techniques will be to aid human beings, in reducing genetic disease and its affects, and possibly improving the human race (Brody 1981). We are rational beings and we should take advantage of the chances used to apply our rationality to the control of something so important as the generation of children, and to agriculture and environmental modification. We have allowed many people that have genetic disease to live, and so have exposed the human race to genetic decay, for example diseases like diabetes are increasing. This is seen as a bad affect on the human gene pool, and something to counter.

Against genetic engineering are arguments such as it is unnatural. We replace natural procreation of human beings. We will always be unsure of the longterm affects of our manipulations, and they may cause harm. We are still ignorant of the mechanism of gene action, and living systems are very complex. The misuses of genetics in the past, illustrated how bad values may be propagated, and these techniques could be abused in the future. There are more important uses to put our resources into than into genetic engineering. Some object by saying that the means may be immoral, such as procreation independent of natural processes, and the loss of embryos. Although much work in genetic engineering has involved microorganisms and recently plants and animals, much of the anxiety concerns

extrapolations to humans. All of nature is important, especially with an ecological awareness, but because of the fears relating to humans, we will particularly look at issues that relate to human beings in this chapter.

"We Should Not Play God " is a very common phrase, but its connection with genetic engineering is not as clear as opponents claim, as discussed in chapter 3. For one thing, if we consider "God" to mean we should not intervene in the processes of nature, as it often does, then it is wrong, as this philosophy rejects modern life altogether, along with medicine and most agriculture also. Another slogan has been "It's not good to fool Mother Nature", however it is quite good to fool nature when treating disease. While there may be a boundary to our intervention in Nature, it is not based on the idea that it is intrinsically wrong to use or change nature, including using genetic engineering. In most religion's the pursuit of health and food of some sort are essential goods.

Related is the question of whether we are creating new life forms. This is somewhat misleading, as while we can produce organisms with new characteristics there is already a long history of human beings directly and indirectly producing these. We have breached species barriers often in agriculture. There are natural mechanisms to transfer DNA between not just species but entire kingdoms of living organisms, such as from yeast and eucaryotes and bacteria. Our recent knowledge suggests that it is less unnatural then we first thought, which also decreases any objection to the modification of living organisms based on this type of argument .

Genetic Selection

The techniques available for aiding reproduction make genetic selection more powerful than in the past when infanticide or sterilisation or selected mating were the only alternatives. We have considered the question of mass screening of potential parents, in order to detect any disease-causing genes they carry before reproduction. People could voluntarily refrain from reproducing or alter their marriage plans if they carry a designated disease. When one of the couple carries a serious genetic defect IVF or artificial insemination, by donated gametes, could be considered. However, there is a "slippery-slope" from the decision of using gametes donated by an anonymous donor, to the case of using gametes selected from people of chosen "quality". There have been babies born from women using AID to conceive their eggs with sperm from Nobel prize-winning scientists. It is also possible that eggs will be donated. Ethically these two alternatives are similar. The limited resources for IVF may mean that IVF is not used currently except for helping the most needy cases.

One of the major arguments against the specific selection of gametes from a donor because of their desirable trait(s) is that we would be aiming more at the biological quality rather than the children themselves. There is a difference between choosing a donor because they are especially intelligent, or good-looking, and choosing any acceptable donor for having children. Because people can use gametes from a person that does not carry a serious genetic defect, does not mean they should choose their favourite scientist or politician, as a donor. There are sperm-banks already being built up, so that this is possible, and some are commercially operated. Verbal genetic history's of sperm donors are made to try to

exclude donors that have some genetic diseases. A physical examination and laboratory testing is recommended by the American Fertility Society. As new techniques arise, there will be many more diseases which can be screened against. Both verbal and cytogenetic screening has also been used in the French CEGOS AID services (Selva et al. 1986). It is ethical to ensure as far as possible that possible donor sperm and eggs do not carry a genetic disease. Currently the burden is on the practitioners and subjects of such studies, but in a sufficiently dictatorial society this could be unethically abused. Since however many other scientific techniques could be abused, this may not justify not using it.

The wrongness in this is not so much the use of good donors for sperm, but the presumed relationship between the quality of the child to be (which may have a higher I.Q. or quality than normal) and its status as a human being makes people consumer products. The Nobel Prize-winning scientist Herman Muller concentrated his efforts on voluntary positive eugenics, founding a term "Germinal Choice", which he thought was an extension to birth control used in reproductive choice. The major method for this was artificial insemination using donor sperm (AID), but instead of the donors being anonymous he advocated using selected donors (Muller 1935). The number of children born by AID in USA is large (CIBA 1973), with at least 300,00 births, so it would be a major selection if employed. The characters he chose in a donor were good health, high intelligence and socially responsible cooperativeness. Some of these characters changed with time, as did the list of his examples of men, at one stage including Lenin, but during the Cold War this changed. The so-called right to procreate, may lead to procreative autonomy, the right to take positive steps to enhance the possibility that offspring will have desired characteristics (Robertson 1983), is a rephrasing of Muller's idea of germinal choice (Muller 1960).

While small scale AID to overcome infertility might not have any detrimental effect on general human reproduction or procreation, large scale attempts at genetic manipulation pose a potential threat to society. This is not like the use of negative eugenics by genetic screening for disease carrying genes, but would have a more dramatic effect on our reproductive patterns, especially in those countries where random mating occurs. We do not know the longterm effects of positive gene selection. There have been strong protests against the use of genetic engineering to alter the germline of humans, such as those led by activist Jeremy Rifkin, because of the fear that they will be used for eugenic ends (Norman 1983, Rifkin 1983). Selective mating for genes is very different to the selective mating that occurs for personalities, or familial social status. There are a few examples of restricted mating patterns among royal families, which are generally recognised as being detrimental to the children's health. This highlight's a need to use gametes from a single donor only a limited number of times, to avoid the possibility of half brother-sister marriages.

IVF, egg donation, AIH, AID, or surrogate motherhood; which can enable infertile parents to have children, can also be used for eugenic selection (Glass 1972). While there may be many cases in which these new reproductive technologies may be used for their primary purpose, there are additional ethical problems associated with their application to positive genetic selection. We considered the ethics of using extramarital gametes in chapter 11. The techniques of AID and embryo transfer might be ethical in some circumstances. The choice of the

donor and the donor's anonymity is one of the problems of the technique. It is ethical to check that the gametes are not carrying some genetic disease, and is unethical to use them without checking if the screening capacity exists, however, it is a very different case when the couple are carrying a high expectancy of having a child with the donor's "excellent genes". Any positive selection scheme would also have the associated problems of high parental expectancy of good genetic children, the child-supermarket problems.

Antanasio (1986) considered the example of a new company that discovers a novel drug that can be used to develop stronger, more intelligent human beings. However, this drug is very expensive, and limited to a few cases. If the government banned the use of this drug would it violate the liberty of people to use it? Banning this treatment would not interfere with reproductive freedom, as the parents can still have a child using normal methods (or nonselected sperm for AID). It would be consistent with the idea of freedom to chose children's education, but it is not inconsistent to ban this drug as the decisions are at different stages of life. The children do have liberty interests, as argued in chapter 13, as genetic freedom. While we may promote the free-will or liberty of parents, we may restrict the "freewill" of the children who must conform to the expected pattern.

It would not be ethical to use donated gametes when the parent's own gametes are fertile and do not carry an untreatable genetic disease, because it is interfering unnecessarily with normal reproduction. It is possible to purchase sperm from donors of known characteristics in the USA. The parents may desire the donor's physical characteristics to be similar to the husband, so that it is difficult to notice that the child is from extramarital gametes. This could be ethical if it is to protect the child until they are mature enough to be told of their genetic origin, however I do not consider it ethical to hold the child permanently in a deceitful relationship. Sperm banks, can also carry information on the educational and intellectual level of the donor, which can aid selection of gametes from donors of higher intelligence. It could be ethical if the parents do not expect their child to be very clever, as the children will probably not be, but if they are expecting a very clever child then proper counseling is required and it is very doubtful whether this sort of selection is ethical.

Germ-line Gene Therapy

Somatic cell gene therapy concerns only the individual treated, assuming it is safe, and is up to personal self-determination, or traditional forms of consent giving. The replacement of a defective gene by a normal one by somatic cell gene therapy still leaves the problem that we need to modify our genotype to improve the situation for long term. However, germline gene therapy involves all future offspring in a more direct way. The immediate concern must be whether it is safe. There may be harmful effects in the future generations. We have the ability to transfer genes, but we still lack the knowledge of the resultant gene transfer. This is especially so for a future person when undergoing full development from an embryo to adult, when different genes and regulatory sequences are used. Researchers should use experience combined with imagination of possible consequences. There are also new genetic techniques for positive gene manipulation. These would allow the

treatment of sufferers of genetic disease in extended ways to our already major treatment of the symptoms of genetic disease in medicine.

Although germline gene therapy is not yet safe enough for use, we must consider technology before it is ready to be used, when it has such major consequences. In the last decade discussion of genetic engineering and its implications was often shrugged off, using those reasons, however, we have seen such rapid developments in technology we cannot predict when pressure will grow to use this technique. Other issues may be more pressing at the moment, such as provision of genetic screening services and privacy of genetic information, but the long term nature of genetic manipulation of the human germline must also be discussed.

Techniques for Germ-line Alteration

There are several alternative strategies for alteration of the germ-line. Most commentators have concentrated their attention on those techniques which are able to provide precise gene replacement or insertion. While this is the ideal case, and will no doubt become possible, we should rather concentrate on the underlying goal. The goal is to obtain normal gene expression that is safe to an individual who would not otherwise be healthy. There must be no negative side effects. While this may be obtained by precise gene replacement, it might also be obtained in other ways.

There are two stages at which the human germ-line may be altered. One is at the level of the germ-cells, eggs and sperm, which could be altered in vivo or in vitro. The other stage is at the embryonic stage, which would be in vitro. I will consider the case as being one which is aimed at correction of a genetic disease, though the techniques are only limited by the genes that we have DNA probes for.

The safest form of germ-line alteration would be the removal of all cells containing the targeted gene. This would ensure that only the cells containing the good allele of a gene were present. This could occur through a targeted gene probe attached to a lethal piece of DNA. Once the probe reached the cells, it would affect only those cells that had the chosen gene, and would not affect the healthy cells. The converse approach would be to target cells which had the good gene, to protect them from a general elimination of germ cells. The germ cell stem cells are diploid, and could contain both a good and a bad allele, so this approach would not be effective.

Much current research has focused on the use of retroviral vectors as methods of targeted gene modification (Friedmann 1989). The germ cells could be altered if the DNA vector spread to many tissues of the body, either non-tissue specifically, or specifically. Since the adult may suffer from the disease, and the procedure assumes the gene is safe, a general body cell infection may be adequate.

Microinjection of Eggs and Zygotes

Microinjection of DNA into eggs is a technique with much animal experience, but the treated eggs still have a low viability. The most common procedure for gene transfer is microinjection of the DNA into one of the pronuclei of a recently developed zygote, which is transferred to a surrogate female for rearing. Generally about 1-4% of the injected mouse zygotes result in offspring with the gene integrated into the germline and capable of being inherited as a simple Mendelian dominant (Palmiter & Brinster 1986). It was reported in 1989 that sperm cells could

take up DNA and produce transgenic mice, at a success rate of 5% (Lavitrano et al 1989). However at the time of writing this had not been repeated, so there are doubts about this technique (Beringer et al 1989). There are other techniques being developed such as the use of laser micropuncture of the cell membrane, electroporation, and biolistics (using high velocity tungsten microprojectiles containing DNA). These techniques are applicable to germ cells or the preembryo.

To use the procedure at the preembryo stage has the advantages that fertilisation has already occured, and a germ-line that exists is the subject of the work. There are techniques that increase the chances of fertilisation of a particular egg or sperm, such as injection of the sperm into the egg, but the preembryo is a desirable stage for any screening. It is after crossing over of the germ cell's DNA, which could produce further gene mutation. The embryos could be fertilised in vivo and flushed out for screening, or IVF could be used.

The genetic screening would also be a prerequisite to any therapeutic uses of germ-line manipulation. Only if the embryo requires gene correction would it be subject to that. Then the techniques of gene insertion could be used, or the fusion of the affected embryo with an embryonic stem cell line containing the normal gene. Using an embryonic stem cell line that had the necessary genes you could always guarantee the presence of the basic healthy genome.

Experiments involving animals using germline gene therapy have been underway for a few years. In the initial demonstration of the use of the technique the human genes for growth hormone and a regulator were inserted into mice embryos and were expressed in the recipient mice doubling their body size. Germline transmission and expression of inserted genes has been possible in animals since 1982, however these crude methods involving multiple copies of genes are not applicable to humans. Only targeted gene replacement should be used. Also the technology still has a high failure rate in terms of the large losses of egg cells, and the failure to achieve any expression. There are major difficulties in the technique if applied to human embryos to avert the expression of a recessive mutant gene, especially in selecting the correct embryo for use. Also the response rate is low for embryos. With the way genetic information is transmitted in humans the genetic disease may not be expressed in the children, as they will only receive one of their pair of genes from the affected parent and would only be a carrier of the disease.

Experiments on animal models are a prerequisite to experiments on humans. One of the animal systems for gene therapy was that of Mason et al. (1986). Mice that were lacking the gene for the synthesis of gonadotrophic hormone releasing hormone were used in trials, in which DNA containing the correct gene was injected into fertilised eggs. The successfully treated animals were normal. Analogous experiments for other genes have been performed. It is unlikely that therapy originating from DNA injection into fertilised eggs will be considered as a means of restoring a deficient genotype in human (Charlton 1987) unless the genes can be targetted more specifically. It is also of limited usefulness, as it may be better just to avoid using gametes that have a genetic disease causing gene.

With microinjection, the transferred DNA inserts at a chromosome breakpoint. This is usually a single random site, and at this site there may be one to several hundred copies of the gene inserted. Only occasionally is more than one integration site observed. Homologous recombination is a desirable technique, as it

involves the matching up of specific DNA sequences and the replacement or insertion (Figure 2-5) of a piece of DNA. The modification of genes by homologous recombination is commonly refered to as gene targeting (Bollag et al. 1989). It has been found that the gene targetting frequency in mammalian cells is independent of the number of target sequences present in the genome (Zheng & Wilson 1990). This means that the actual search for a specific DNA sequence is probably not the rate-limiting step in the process. In yeast cells however, the number of target sequences does affect the frequency of homologous recombination. The proportion of recombination events that are homologous, as opposed to non-homologous or random, is lower in mammalian cells than in yeast. The technique utilises natural cellular processes, and the experiments will help elucidate the natural processes of DNA repair.

Embryonic Stem Cell Lines

The way to get targeting is to include a homologous length of DNA in the insert compared to DNA at the desired chromosomal site. The frequency of homologous recombination occuring is between 1 in a 100 to 1000, and improving (Bialy 1990). To use this technology, it is easier to insert the gene into cells and screen the cells for successful gene targeting. Embryonic stem cells can be used, and only when one cell line with the desired insertion is obtained will it be inserted (Capecchi 1989). ES cells are preimplantation embryonic cells that can be maintained and genetically manipulated in culture, the selected cells are used to generate germline chimeric animals.

Gene targeting means that it is now potentially possible to generate mice of any desired genotype. ES cell lines have been used to create germ-line chimeras containing targeted gene alterations in the HPRT, ab 1, en -2, n-myc, B-2 microglobulin, igf -2 and int -1 genes (Capechhi 1990). They are very useful for the study of new methods of gene targetting. Methods to increase the ratio of homologous to nonhomologous recombination events are being developed (Bollag et al. 1989), Capecchi 1989). The frequency of successful homologous recombination must be increased if other methods are to be used.

It is possible that human chimeras could be made as a form of treatment for recessive diseases so that you could always guarantee the presence of the basic healthy genome by using a standard embryonic stem cell line, this might be more technically feasible than the alternatives. The capacity exists to make different human embryonic stem cell lines, it would just require making one without disease.

Health and Disease

We may aim for positive eugenics, but the judgements "healthy" and "unhealthy" are not clear if an extension is made from phenotypic symptoms to genetic (WCC 1982). What we need is to distinguish between eugenics, the selection of good genes and what we could call xialiogenics, or selection of healthy genes. We could split these new techniques into therapeutic and non-therapeutic (Fletcher 1983), with narrow boundaries (Leenan 1988). Non-therapeutic would include eugenic aims or enhancement (Anderson 1985). This distinction is more important than whether we are adding or subtracting genes. However, some argue

that nonmedical reasons may also be ethical. If we accept it is good to correct a genetic disease, than we may also argue that it is good to improve our ability to resist cancer, it may also be good to increase our intelligence. The question is where do we draw the line?

The lack of a clear borderline between therapeutic and desired treatment is not just found in the question of using genetic techniques. It is also seen in the use of cosmetic plastic surgery, which can be used in extreme ways to change body appearance. Another example is the use of growth hormone treatment, where it should be given to dwarfs to become normal size, but can also be abused to make normal children grow to be very tall to aid their sporting potential. There are short children who are not deficient in growth hormone. The question is whether short statute is a disease. There is one medical argument for treating them on an association between shortness and psychological morbidity. But it is not sure whether growth hormone treatment will reduce this morbidity. Each individual will be different, and some other studies suggest that growth hormone does not relieve psychosocial problems in growth hormone-deficient children. There are serious doubts as to whether it will work. Also the treatment is expensive, currently costing US$20,000 per year for a 30kg child, who normally requires five years treatment. To treat those in the lower third of the height distribution in the United States would cost US$10 billion a year. The experimental and economic arguments are against this extension of using growth hormone (Lantos et al. 1989).

There are more medical therapies that will need to be considered, such as the alteration of genetic risk factors for disease, such as eliminating hypercholesterol levels in people so that they do not have a high risk for heart disease (Anderson 1985), or treating some genes that cause a disposition to certain cancers. If we spend large sums of money on increasing education and make children work very hard at school, to the point that they lack social interaction after school as in some countries, is it not better to aid their education by drugs or eventually by genes? The answer is probably that it is better not to expect such high standards. After spending time with some people of supposed high intelligence I would say that it is a goal that has got out of hand in many societies. It is also very dangerous to correlate the action of certain genes with very complex psychological attributes, such as behaviour. It takes attention away from the major social causes of such problems.

If we could insert a germline genetic alteration that would act as a vaccine against important diseases, such as Hepatitis, Malaria or AIDS, would not these be justified. Even more so if a genetic vaccine for the diseases of the developing nations could be developed, and effectively delivered. Given that the economic inequalities may not change, it may be the only way to reach the majority of the world's population. It would also have strong reasons for universal application, like the eradication of smallpox. People must think very seriously when they tend to sweep any notion of germline genetic manipulation under the carpet. We need to think of using any technology that may provide benefits, only after doing so, will we be in a place to ethically reject or accept it. If such a scheme is permitted, it should be distributed justly, and fairly to all.

Carriers of Harmful Alleles May Be "Healthier"

The concept we need is selection of health, though in a narrower sense than the World Health Organisations criteria of health, referring rather to the absence of

disease causing genes. While a person may look healthy, we all carry up to 10 recessive genes, which if matched up to another allele to form the homozygous condition would produce a lethal disease. A further problem is the difference in the phenotypic states between those people of heterozygous and homozygous (two copies) state for certain alleles, e.g. in sickle cell anemia the homozygous trait is lethal, but people in the heterozygous state are more resistant to malaria. The result is a much higher level of this allele in people of central Africa where it has proved advantageous to carry this allele as it confered resistance to malaria, even though more people die when born with the homozygous state. The percentage of sufferers of sickle cell anemia in Central Africa compared to North America are 2.5-8%/0.3-1.3% , and the percentage of carriers of the allele are 30+%/10% respectively.

Sickle cell disease is a classic case but other examples have been found. The heterozygote form of the recessive gene for congenital adrenal hyperplasia appears to protect Yupik Eskimos against infection with Hemophilus influence B. The Tay-Sach's disease-causing allele appears to confer advantages against tuberculosis, and several similar lipid-storage diseases may also have advantages if suffering from tuberculosis. A different type of compensation is seen in idiopathic hemochromatosis that is found at a heterozygote frequency of 10% of the population of Europe and America. The abnormality results in increased iron absorption, which is an advantage for women, but not for men, as it can be fatal. The high incidence of insulin-dependent diabetes seen within a few decades after the people carrying the disorder (Yemenite Jews, Pima Indians and Micronesians) shifted to a Western diet after previously living in conditions of food scarcity is another point. The disorder is actually an advantage if under starvation conditions, but a disorder with a different diet (Rotter & Diamond 1987)

Another disorder is glucose-6-phosphate dehydrogenase deficiency which increases resistance to malaria, and is harmful only if eating fava beans and when taking certain drugs. These examples must make us look carefully at categorizing disease. It is difficult to draw the line sometimes, so that an arbitrary barrier may be needed. There are strong arguments on a secular level, including the discussed uncertainties of manipulation, to make large scale eugenics ethically undesirable. But we may still feel that if it is possible, it is better to start helping people come into the world healthy if we can do so at some point in the future.

Spontaneous Mutations Will Continue to Occur

The total elimination of all disease-causing alleles is an unrealistic goal, and is unobtainable. It is not possible to erradicate genetic disease completely as many people are carriers for genetic disease and are not aware of it, and many occur spontaneously as new gene mutations in the parents' gamete producing cells. One third of hemophilia and two thirds of muscular dystrophy are the result of new mutations. Studies with gene-specific probes have demonstrated that the mutations resulting in a particular phenotype are highly heterogeneous as a group (Davies & Robson 1987). So even in diseases where the natural mutation rate is very low it is sufficient to maintain a rare stock of these altered genes. The amount of these natural mutations increases as we are exposed to more environmental hazards from pollution.

Elimination of disease-carrying alleles is not necessary for the health of the

population if genetic screening and therapy is available. It is also important to recognise that germ-line engineering will still not solve the problems of genetic disease. Every generation will have this problem, which may need the use of embryo screening, to detect those individuals conceived with a new mutation, and the future development of medical therapies.

Human germline gene therapy is not currently legal in the USA (RAC 1986) and some other countries, but it is viewed as one day becoming appropriate, in some cases. There will always be a need for somatic cell gene therapy anyway, as it can be performed on individuals at any stage of development, while germline gene therapy needs to be performed on either the gametes at an early stage or on the very early embryo. A certain type of somatic cell therapy can be envisaged that will modify all cells of the body, including gamete-producing cells, so that the next generation could be treated, but the large number of spontaneously occuring cases could not be.

Ethics of Germline Genetic Engineering

We Already Change the Genes of Children

Although we may feel very uncomfortable at the idea of altering genes, we should be clear on one thing, we all do it. We decide to bred, or not to, and how many children to have, and who to get married to. We do not like disease, so we try to treat it, and most parents would replace a deleterious gene in their children to be if that would save them from illness. There is no medical reason not to replace disease-causing genes with normal genes to avoid disease in future generations. It is clearly different to the type of eugenics that people object to, it is rather xialogenic.

Some argue that we should not remove a gene from the population because it may later prove to be useful. If we take the case of sickle cell anemia as above, if people are carriers of one healthy and one diseased allele than there is no effect on normal life, unless you are present in malarial areas; but if two carriers marry than they have a one in four chance of having a child that will die from the condition. The alternatives for those parents are several, they can have premarital screening and alter their marriage plans, they can have genetic screening of the embryo and selective abortion, or in the future have gene therapy of the somatic cell type on any affected baby, or have germline gene therapy. Once the technique of germline gene therapy is satisfactory then it may be the best alternative to preserve their choice of marriage partner. The choice of a marriage partner should be based on personality compatibility, and love for each other, rather than checking through a list of suitable gene donors for procreation. The harms from not eliminating the disease carrying gene are greater than the possibility that the trait may avoid malarial infection, at least in countries where malaria is no problem. In fact current antibiotics and sanitation have been much more effective in protecting the same populations who have sickle cell anemia, from malaria. If we are worried about the loss in genetic variety, then we should not be, as there are multiple forms of healthy genes existing anyway, what is called polymorphism. There are several possible healthy alleles for many genes, yet all are functional, so that could preserve genetic variety to maintain the diversity of genes that might be needed for future diseases (OTA 1987a). There are

at least 46 distinct alleles of the gene phenylalanine hydroxylase (a mutated allele is responsible for the disease PKU). We do not violate any "rights" of future offspring by removing harmful genes, rather they will be grateful that they do not suffer from the disease, the same as if they are treated by medicine when alive. There will be plenty of nongenetic diseases to suffer from even if we can remove many genetic diseases.

The objection that we would be Playing God reminds us that we do not know enough to change any genes except those that cause disease, and should not go beyond that. We need to examine the whole of modern medicine, along with the reason why many diseased people live. It is because of much life-sustaining technology, which is a half way solution to the problem which in certain situations can appear to be worse than non-treatment as it only provides longer life without any cure or treatment. We are already intervening in nature, but not well enough. As a precaution, we could change only one allele when performing germline changes, so that genetic screening could be used for the next generation if something went wrong with the gene, so that the rest of the genome could be passed on. Though if we possess the techniques for gene insertion we would also be able to alter the gene in subsequent generations.

Some think that characteristics such as personality and intelligence are probably outside the potential of gene therapy control, and there are other simpler measures which any insane individual dictator could use (and have), such as drugs or sociological pressures, to control society (Cherfas 1982). Some scientists believe that we will only be able to change human phenotype in small ways by genetic manipulation, less than we can by social and environmental influences (Rose 1984). Fear of genetic manipulation owes a great deal to the excesses and associations of eugenics (Kevles 1985, Nossal 1985, Ledley 1987). A principle of human life held by many to be fundamental is that there is a right for men and women, with regard to their fellow human beings, to have the choice of their own partner in marriage and to decide whether they should reproduce, and this can never be overruled by considerations of their class or their religious outlooks, or on economic or biological grounds. The government may offer incentives or discentives, but those policies are for society as a whole and should not be in breach of human rights. There are already genetic screening programmes used by some employers and insurance companies as we discussed in chapter 13. This does not imply that people have a right to use any technological means to alter the genetic characteristics of themselves or future children.

We may ask, is it worthwhile to use these techniques? Why should we try to fix the germ-lines of a few, why not just encourage the use of donor germ cells and avoid the use of defective germ cells altogether. This may work on a small scale, but if we consider the fact that every individual carries a dozen or more alleles that cause genetic disease, than we will still be using germ cells with potential for disease. A carrier of a recessive allele for a genetic disease is the normal situation of every individual on this planet, something that should be a basic piece of information for anybody undergoing genetic counseling. It is not the objective of germ-line engineering to change this, rather the realistic goal is to have healthy people, as stated above. It is an impossible goal to fix all the potentially disease causing genes and those who start the "game" should know the limits.

The idea of genetic health is implied, but it turns out to be very difficult to

define. It is possible for an individual to have many harmful recessive alleles, but to be phenotypically healthy. In fact we are all estimated to have perhaps ten recessive alleles that would be lethal in the homozygous state. To make it more complicated in the heterozygous state there can be advantages to possessing one of these bad alleles. The health of any complex organism is the result of many interactions between genes and the environment, and health is a concept that should apply to the system as a whole, whether it be cell, tissue or being, but not to the genes. One of the goals of eugenics is to improve the genetic health of the population, but this is impossible to specify. However, there is still a question of the individual's duties to society in their reproductive choice, which is a fundamental issue. Rather medicine has to consider improving the health of individuals which will include some genetic therapy when possible.

Consumer Children

This is a more realistic objection to the new technologies, and we have seen the emergence of commercial surrogacy as a prime example of this. It could also be said of private IVF clinics which are making a profit on providing this medical service. It is a very sensitive area, and is related to the feeling against slavery of human beings, and the growing influence in society that says that we can buy anything if we have the money. There is also the issue of chosing the desired characters in a child, that will be possible in increasingly more precise ways. This is a more important issue, and has a new element. It is one thing to chose the spouse because of the characters that they have which one hopes will be passed to the children, and to be a parent to our children, but another to actually select the child. There are long traditions in different cultures that involve careful scrutiny of the relatives of a marriage candidate in the selection process, so that relatives of epileptics or people of genetic disability may be selected against, particularly seen with Jews or in Japan. These may have been developed to protect these ancient societies eugenically, but are not longer justified because of modern medicine and genetic screening.

If genetic engineering and genetic selection allows parents to pick and chose their children, then it encourages the replacement of personal and permanent family relationships with instrumental and impermanent relationships (Brody 1981). The social consequences are very important, but may be hard to determine (Weatheral & Shelby 1989). The relationships in a family are unique in that they are personal, permanent and are not chosen by the parties. Divorce can undermine this, which is also a bad influence. We are always in the relationship just because of being a member, we do not have to prove ourselves as we do in other relationships. Family relationships are mutually supportive. Instrumental relationships are the normal outside of the family, we value other people for what they can do for us and their roles. There is an implied threat that if parents chose a certain type of child, then if the children do not perform they will be rejected. This tendency is a real danger in countries where prenatal screening is being used for trivial conditions, such as sex selection. Even if the character chosen is a primary good such as intelligence, it is good only in certain careers to have exceptional intelligence. The parents should be bringing up the child to develop their individual autonomy, and should not impose parental expectations on the child.

Behind the idea of defectiveness is the image of a perfect human being, but

we should be clear that we can not be. There is a growing idea that we can improve the human species, and that we can improve on nature. Attached to this is the idea that we can alter human beings morally by altering them biologically. The idea is that we need to increase human quality (Fletcher 1988).

Slaves to the New Technology

We have changed society dramatically in the twentieth century by the pasteurization of milk, sanitary food, antiseptic hospital conditions, compulsory immunisation programs and antibiotics. Though these are still to fully reach many people in 1990. While there are still major infectious diseases, for instance 1500 million still are exposed to malaria, in many parts of the world genetic diseases have been highlighted by the control of infectious disease. There is now the philosophy that since we have got rid of some infectious diseases, such as smallpox, we should work to eliminate genetic disease. Children may be produced in a quality control environment, with special characteristics, or else the fetus may be eliminated before it grows into a child. We need to concentrate not on a continued push of technology for itself, but rather for the benefit of individual patients.

While rationality is a high human virtue, it is a contentious matter as to whether it is the highest human virtue, there are many others that are often considered higher, such as love, charity, joy, ability to live peacefully, variety of people, and many culturally dependent virtues. If a new technology becomes available it may not be the most rational course to use it, and even if we do embark there are often hidden dangers. Related to this is the general theme of science as a means to Utopia. There is a major feeling that the progress of society can occur together with scientific advance. However, there will be points where scientific progress will not improve society, and there are already many who think that we have got worse in this technical age. Genetics is far from being unique as an element of social change, there are many others that appear permanent and have ill effects such as the centralisation of commercial shops with the disappearance of local shops, the growing addiction to watching television, and the dangers of the computer revolution.

While the ability to pick and chose our children can have a damaging affect on our attitude to children, it can also have a damaging affect on the autonomy of reproductive choice of parents. While there may be a right to free choice of marriage partner, and this should never be compromised in a society that respects the autonomy of individuals, there is not an unconditional right to bring up children. If parents miss treat the children and abuse them, they will be taken away, for the best interests of the child. However, what about the right to bear children with genetic disease. This is a very contentious issue but one that is arising. Earlier in this century it arose with the compulsory sterilisation programs of USA or some of Europe. Britain did not authorise such a sterilisation program, but did prevent marriages, which could be argued to be more of a violation of rights. However, the extent of the sterilisation programs and the racial ideas which were behind much of them is a much more vivid memory. The rejection of these programs was due to two things, one was the lack of scientific evidence for the disease conditions, and the other was growing awareness of the rights of individuals and the excesses of the Nazis. However, today we have growing scientific basis for some of the genetic links with disease, and so the only barrier to a return to compulsory eugenics is a

recognition of the autonomy of individuals.

The mechanism of selection can be voluntary also, by subtle propaganda and by medical insurance schemes which indirectly enforce cooperation. There is certainly a responsibility of good parenthood, but like other issues it is a moving line. There is a long history of parental responsibility in passing on education, some material wealth, and providing care for children born. There will also be responsibility to ensure the health of the fetus to some degree. This however can become restrictive on the adult, which affects the pregnant women, and the medical interventions that are recommended. There is already the knowledge of behaviour that is detrimental to fetal health such as smoking, overdrinking, or many drugs (both legal and illegal), yet enforcing strict behavioural regimes can intrude on a women's autonomy. Of course mothers want there children to be healthy but there is a limit. We need to question what is the goal of society. For several decades after World War II there was a feeling that science and technology could provide everything, and they should be promoted. Many saw that only science based technology could change our society for the better. However, during the last two decades there has been a growing feeling that technology has actually led to many problems as well as benefits. There has been a growing and strong anti-technology feeling (not so much a anti-science feeling) (Cavalieri 1985). Scientists assume that science is naturally good for society, but this is not an unconditional assumption.

We should remember the parallel between biotechnology and computers also, both are thought to give rise to major changes in society, and they are both having some impact. In the early days of the computer revolution the computer was going to change radically every aspect of human life if some people were listened too. But today we do not hear so much about this, though I doubt it is because it has lost its potential power for change, but rather that society has accepted the changes so far, which for most people have been for the better. However, with biotechnology we are dealing with the complexity of life itself, which may have greater potential. It has also begun, and society is accepting it and society will continue to change. There is a need for more consideration of the way in which society changes and whether this is for the better or not.

Protecting Future Generations

We are often uncertain of the precise outcome of interventions in nature or medicine. Fortunately nowdays most are ready to admit that uncertainty, which while being the norm in medicine, has taken major ecological disasters to convince people in industry or agriculture. We will never be certain to have complete control over the effects of introducing new gene sequences, and with many cases much further experimentation is required before we will be able to ethically allow full scale use of them. Ignorance of the consequences means caution in using new techniques, and this is an approach seen in the regulations governing the use of human gene therapy.

There have been regulations and legislation brought in which oppose the use of germ-line manipulation. Some of the restrictions apply only to procedures other than to cure a hereditary disorder, but others are more general. The British Human Fertilisation and Embryology Bill would outlaw germ-line gene therapy on embryos. The European Council has passed a recommendation stating that every new individual has the right to a genetic constitution that has not been interfered

with. In 1988 the European Medical Research Councils issued a joint statement stating that "germ-line gene therapy should not be contemplated", neither should enhancement genetic engineering (EMRC 1988). In the USA germline gene therapy is not considered yet, but may be so at a later stage. The National Health and Medical Council of Australia Report stated that germ cell gene therapy is ethically unacceptable. In the state of Victoria, Australia, it would be illegal. The reaction against germ-line manipulation has been widespread. The International Organisation of Scientists for Social Responsibility has proposed that the United Nations add an article to the Human Rights articles, saying that a human genetic inheritance should not be modified, except by using somatic cell gene therapy. However, while the technology is not sufficiently safe to predict outcome gene therapy should not be used, it does not need to be legislated against before proper discussion has occured. If society can allow somatic cell alterations such as cosmetic surgery, or independent schooling, there may be a case for genetic freedom. On the otherhand, legislation against germline manipulation can be useful as a barrier to hasty use of germline manipulation, as extensive discussion would be required to reverse the legislation and general societal approval would be needed. There is a case for both approaches.

Germline gene therapy involves all future generations. Parents do make decisions concerning their child's health and we can assume that future children do not want to be ill (Leenan 1988). This assumption is already used in some compulsory genetic screening for PKU and other diseases in newborns, and is consistent with good parenthood. However, these decisions are not usually so far reaching. The concern for long range consequences is an important part of contemporary ethics (Jonas 1976). We have a duty to consider the second-order remote consequences of any course of action, when debating the ethics of that action. Ethics was generally restricted to considerations of relatively short term consequences, within the immediate community. Modern technology means that man has become an object of his own power, not with external effects, but internally.

Our decisions can have far-reaching consequences as to the identity of the child, but it is another question as to whether this is important if the same number of children is considered. For instance, if "I" was conceived from a different egg and sperm "I" would be different, and someone else would be in my family who may not be writing this book. But, if I never existed and my parents had another child, would the family situation be very different? They would still have a child, and that person would be of equal value to myself. I could not accuse my parents of having me, as I would never had existed. These types of choices have been discussed by philosophers, and are important for this type of longterm public planning, including the use of genetic engineering on future generations, and genetic screening and selective abortion.

There are different ways in which a given individual might be different from what they are, but the point at which they become a different individual is often viewed as when they were formed from the union of different gametes. In view of the earlier discussion about the status of the human embryo in chapter 5, in particular on the origins of individual life (Ford 1988), rather than concentrating on the fertilised egg or zygote we should focus on the earliest item from which the individual is uniquely developed (Williams 1990). The idea that an individual is principally distinguished by the joining of two unique zygotes, above all other

differences is called the zygotic principle (Parfit 1984). The zygotic principle represents the view that different individual fetuses will be different people, though it does not maintain that a human person is formed at conception, or the formation of the primitive streak, or viability, or some particular point in development (Williams 1990).

If a parent suffers from a serious genetic disease then the child can not be held responsible for it. They may blame parents, or others, such as chemical companies who released poisons in the environment, but we cannot attribute blame to those who suffer from the disease. If we live in a just society we will look after their special needs. However, if the person decides to conceive a child knowing that they might suffer from that disease, which could be detected by prenatal diagnosis to confirm the condition, if they know that fetus will be afflicted, they do have some blame for the child's disease. If they use prenatal diagnosis and find that the first fetus is suffering, and abort it, and have a second child which is healthy they will have good reasons for waiting to conceive a fetus that is free of the disease (Hanser 1990). It is not possible for some individual to say that if their parents had waited until later that they would not be handicapped, as there would be a different individual. In the case of genetic screening, one individual cannot express the concern that 'even if it would not have been them but that the other person would have had a better life', because they do not even exist. However it is philosophically possible for them to say that it may have been better for them not to exist (Williams 1990). However, it is a very different step for this concept to be accepted legally, as in the case of "wrongful life", and it is socially undesirable to do so. If they have the chance to use genetic engineering to ensure that the fetus is normal and they do not, than the parents might be held even more to blame than in the case involving abortion. If the question is one of the parents using genetic engineering to treat the same individual then that individual can say that they would have had a better life as themselves if their parents had used it. The same blame could be attributed to a government that withholds such a technique from being available to the public if it has reasonable resources to implement such therapy. The argument is similar to that used to justify other medical techniques, and when safe genetic engineering is available and a better alternative to other therapies for the individual, than there will be pressure to make it available.

Somatic cell gene therapy will lead to germline gene therapy. With germline gene therapy we may all agree on the treatment for some specific diseases, but there will be a "slippery slope" towards research to modify other less clearly undesirable human traits or even toward modification of human characteristics for malevolent purposes. There are limitations as we may misuse the possibilities offered us as we often have, this is however not an argument against their use, but a reminder of our limitations. We may have to live with the disadvantages to benefit from the techniques. But a danger exists if we do not use germline gene therapy but only somatic cell therapy. Somatic cell gene therapy could not prevent perpetuation of the disease, so the future generation would need to be treated as their parents needed.

Germline gene therapy used for eugenic purposes is in the category referred to by Lewis. (1947), a long-term exercise of power which means the power of earlier generations will be over the later ones. The last men, will not be heirs of the power but will be of all men most subject to the great planners and conditioners of the past. An "advance" such as this leaves men weaker, as well as stronger. Technology

seeks to do or to act rather than to merely understand genetics, and hence is associated with power. The power will be held by a certain portion of the population. This power has long range consequences as it is not confined to the present people, but extends to future generations. Although each generation does make decisions that affect the next, the type of affect that they have had in the past have been restricted to the type of political system, religion, cultural value system. During the last century we've seen more dramatic changes, such as brought about by the industrial and scientific revolutions, and global changes to the environment such as the Greenhouse Affect or depletion of the ozone layer. However, genetic manipulation is a more direct change then these, as it alters ourselves directly. The category of decision may not be completely new, but the consequences of the decision to human beings are certainly greater. The problem of policy becomes one to ensure that the powers which are accruing to some individuals are not abused.

Shirmacher (1987) argues that with the use of genetic technology man has become homo generator. We no longer have to settle for what we are given, instead we can alter the "fundamental building blocks" of life. People may denounce this new role, a reason for the great concern about genetic engineering, but he sees it as consistent with our role in evolution.

It has been claimed that genetic engineering is like nuclear science, as both confer a power on humans for which they are psychologically and morally unprepared (Cavalieri 1985). Certainly biologists claim that they can outdo evolution, and use genetic engineering widely; but the question is whether we are ready for this new power. In the 1940's we learnt how to use nuclear fission, and physicists initially motivated by the aim of developing a weapon to use on fascist Germany, became so wound up in their work that they did not slow down when they knew it would not be needed. After our experience with atomic power we should face the biological revolution with our eye's open, the question is whether we do.

Another question is in whose hands will the power be, with the scientists or under commercial control. While scientists might be able to retain control initially, it is very likely that like all developments involving much commercial interests, the commercial interest will dominate. Much of the research in these areas is paid for by commercial companies, even human gene therapy has commercial backers. Genetic screening tests are being commercially sold, medicine is very big business, as we already know from the huge number of duplicate drugs and the pharmaceutical companies.

In our commercially minded world it is not surprising that many companies have invested much in biotechnology and they are beginning to get some of the benefits. Many things have been patented, many processes, including patents for animals. There are some technologies that have not been patented, such as much of those involved with in vitro fertilisation, but other areas are. There are arguments to say that this creates much more research money, as it may, but there are also growing dangers of the control of valuable drugs and technology by major countries. The resources of this are genes, and it is interesting that the major gene banks are controlled by the wealthy countries. As we cause the extinction of many species we lose many potentially valuable genes, so germ storage banks have been developed. The world's genetic pool is under control of these places, and a type of gene imperialism (Rifkin 1985) could develop. We must be careful that this

technology is shared out, as the new agricultural species are most needed in the third world. This problem is not unique to genetics though, and is appropriate to many other areas under commercial control.

Because the changes are not easily reversible, and potentially irreversible, and involve human nature, there are very strong reasons to say that we should not impose the ideals of the genetic engineer upon the future generations. We can see how quickly that human ideals change, over ideas such as beauty, good personality, intelligence level and talents, between cultures and generations. We have no right to set our current ideal of favoured traits for future generations. The great variety of human beings is one of the greatest virtues of the human race, more than intelligence or sporting ability. The variety of people with different talents is essential for human society. We could object to any adjusting of human virtues by imposing fixed genetic blueprints on human beings. We still have power to change the future, through education, and this process will continue. Social ideas should be allowed to develop further without interfering in the process. Ethical arguments join public policy arguments in opposing enhancement genetic engineering.

With all this said, there is still a case for attempting to cure disease on a large scale. It is not unethical to extend symptomatic treatment for disease, to treatment of genes to prevent the disease being passed on. In fact every human being has some recessive lethal alleles, which if paired would cause death, and/or genetic disease. It is practically impossible to erradicate this from the human race, as every new individual produces new mutations (Ledley 1987).

Imagine the situation when we know that some alleles of a gene cause susceptibility to criminal behaviour. We have jails that are full of hardened criminals, some of whom have this gene. Should we change it? Should the sentence be moved from life imprisonment to genetic correction and rehabilitation. The fairest may be to give the option to the criminal to decide, if such a therapy worked. We must be careful in the degree to which we put excuses for behaviour in the genes that people have, but it may well be a major part, together with childhood experiences and environmental reinforcement.

It does not seem ethical under any system of morality to genetically engineer peoples' personalities to the "ideal" image of another person. While it is relatively easy to call a disease a disease, many subtle variations in personality are generally believed to be virtues of humanity given by God. There are limits to the employment of techniques, not necessarily taught by compassion, but by understanding what God has made. As O'Donovan (1984) has said, every technique may need its sabbath rest, a point beyond which we don't interfere but appreciate God's creation. But the possibility could only be envisaged if genetic engineering became widespread and used for treatment of more things than genetic disease. This is something we must always guard ourselves from, but we should not let it limit our therapeutic use of the techniques now.

Positive eugenics through germline gene therapy might seem more acceptable than negative eugenics, or selective abortion used in many cases now, but while we are unsure of the positive outcomes from therapy, selective abortion may be preferable. It may be that our application of life-saving technology is premature, that we should save lives when there is some hope of the life being restored. It can be argued that it is playing God too much to intervene in cases when we can not restore health. Gene therapy is more acceptable than selective abortion if we

consider a fetus of any age to to possess the rights of a human. However, that is not the view expressed in this book of an embryo in the first two months after conception. It could also be argued that the risk to the individual of possible bad consequences after genetic manipulation, especially as the technique is first being developed, is unethical and it is in the best interests of the potential person not to cause harm. The cost of gene therapy is also more important, which is important when rationing health care fairly. If prenatal screening can be performed at 6-8 weeks, which is possible, then it may be ethically preferable. If done later than that time, gene therapy would be more consistent with the view of the human embryo expressed in this book. The best approach depends on the weighing of the relative technical reliability of each procedure, which will change with time.

We assume that future children do not want to be ill, which is justified. This is the assumption used in compulsory genetic screening for diseases such as PKU in newborns. It could even be said to be more consistent to want children not to suffer from disease, and to use reasonable and safe methods to ensure this, than not to use such medicine. However, it could be argued that to interfere unnecessarily with every conception to screen it during the first week to decide whether to use germline gene therapy would be quite unethical, as well as being impractical. If screening embryos from parents who are both carriers of a recessive disease like cystic fibrosis, then one in four embryos would be affected, in view of the other embryos that could be made unaffected, then this is the limit of the interference needed to correct the disease. With the resulting possibilities for "enhancement" of human capabilities by genetic means or eugenics programs encouraged or even enforced by governments. What these possibilities do suggest, however, is that strong controlling committees must be established to control the use of these new techniques to monitor where they are developing. This may help to ensure proper guidance of the use of gene therapy so that it may be more beneficial, and to prevent any misuse through premature or undesirable application. They should also help to generate awareness of the way in which genetic engineering practises may alter social values and important interpersonal relationships. Currently there is little consensus on the moral approach we should use in dealing with germline genetic manipulation (Anderson 1985). There needs to be guidelines and legislation in areas relating to what we can do now, to protect society.

Uncertainties in the techniques may allow for unforseen disastrous consequences, and we will remain largely ignorant about the longterm consequences of altering the basic genetic makeup of our race - but correcting disease only needs the repairing of mutations that have occured, which will not lead to any new problems. There will always be a wide genetic diversity in the many other traits we possess. Suffering can not be erradicated by changing our genes, and this should not be the ultimate aim of medical therapy.

Cloning

After the development of the technique of assexual reproduction of clonal frogs in the mid-1960's there was a period of much debate considering the possibility and ethics of cloning humans. There was increased publicity associated with the now assumed fraud of David Rorvik's book "In His Image" (1978), further

progressing the debate. The topic of cloning was also dominant in Aldous Huxley' s "Brave New World". Of the many types of ideas on the science dominated future of man, the most sensitive area is the things that affect the inner constitution of humans. However, since then most discussions of cloning pass it off as unlikely to occur in the near future, or as improbable. Some recent developments have led to cloned mammals which makes the possibilities for cloned humans much more immediate.

Techniques for "Cloning"

There is an early report of nuclear replacement in mature human ova resulting in cleavage of the ova to the two cell stage (Shettles 1979), but this work has not led to any further published success, as it is often found that a dividing preembryo made in this sort of way will cease to divide differentially and either die or start dividing somatically. There is the reported case of a possible two cell parthenogenetic human embryo that was aspirated at oocyte retrival for IVF (Padilla et al. 1987). It is not thought that any fetuses have developed from such an embryo, and it appears that for proper development of mammalian embryos genes from both parents are needed, as genes are differentially used from paternal or maternal chromosomes.

The use of IVF and embryo transfer has been progressing, and has become well established for human reproduction. Even when Edwards and Steptoe, and others, were developing these techniques, the potential for further applications to cloning was noted by some scientists (Watson 1971). It is certainly possible to split human embryos to provide a cell or two for DNA analysis for preimplantation genetic screening as discussed in chapter 13.

It is also possible to split a human embryo to produce twins, depending on how far they see regulations permit this. From experience with animal studies there would seem little to fear from ill effects on the babies, and identical twins are not unnatural. Blastomeres of early cleavage-stage embryos of cattle, horses, pigs, sheep and mice have resulted in normal development from as little as a quarter of the normal complement of cells. There have been live births of 2-4 clones. Development and the ease of manipulation may be species dependent.

There are human teratocarcinoma derived embryo stem cell lines which could be used in transferring genetic information to human embryos. Chimeras can be produced, and a standard embryonic stem cell line used in many embryos to make partial clones. This is technically possible now. We do not need to speculate on the time such technology will be available any more, it already exists, the only question is when it will be safe to begin, and if it is ethical.

Ethical Concerns

There have been quite a few objections to human cloning. The major one would appear to be that we must be sure that any clonal human when born does not have some defect the result of the cloning process, such as the rules used when we think of gene therapy. The rules used for prohibiting germline gene therapy could be applied to attempts at human cloning, as you could say splitting of an embryo is a genetic manipulation. The problem might be, that preimplantation diagnosis of an embryo by taking one cell away from an 8-cell embryo, might be a justifiable technique, as from the experience from animals there seems little risk to the

offspring. Though also animal embryo splitting experiments have not reportedly produced mutant live births (the embryos may fail to develop in utero if damaged), but better records need to be kept to be sure of this (Monk et al. 1988).

Some object to cloning on the grounds that it is against natural law or is "playing God", as for genetic manipulation in general. The objection is valid to some degree, as discussed in earlier chapters, and more so when we consider human beings. We do use technology in many ways in medicine, and the objection can be overcome if we could satisfy more important questions, the primary one being does it benefit the individuals to be born. However, to the twins made by embryo splitting this objection would not be relevant, as identical twins occur naturally.

There is the objection that it would reduce the genetic diversity of a species if it was made from many clones, but this would only apply if we were making a significant proportion of the breeding population asexually. We should always try to maintain diverse organisms, as they tend to be better able, as a population, to survive major diseases or environmental changes.

There have been ideas of human cloning proposed by some scientists, or extreme philosophers, as being desirable. There have been propositions of the advantages of human cloning even advanced in the Soviet Union, which since the 1930's was hostile to such eugenic ideas. There are not many supporters, but a few (Graham 1987). There is still much reserve concerning any applications of human genetics, and there is still a strong nature/nurture debate, and fears that it would strengthen the elite in society.

Other objections to human cloning such as the psychological problems (Ramsey 1970, Glover 1984, LaBar 1984), it being a misapplication of health care resources, it will change our attitudes to children, and to the way we reproduce (Cherfas 1985), could also be applied to other birth technologies. It has been suggested that it may lessen the respect for individual person's (Chadwick 1982), because of the feeling that they could easily be replaced. These problems are hard to assess, but what appears to be a crucial question is the number of clones. If the number is small, many of these problems would not exist. Having the identical genotype certainly does not result in the same people, as environmental influence appears to be a major controller of behaviour. At least it is sufficient to ensure differences between genetic clones. We do not call identical twins clones, even though genetically they are. They are obviously very different in many cases.

There is still concern about deliberately creating identical humans, and the Council of Europe has recommended that creation of identical twins after IVF be forbidden as discussed in chapter 5. However, if we can satisfy the criteria that the individual will not be damaged because of the technique, it would not be a major step to use embryo splitting after IVF to implant twin embryos. This might be especially applicable to patients who use IVF and preimplantation diagnosis for genetic disease, so that the preembryo found to be free of the defect could be split to improve the chances of embryo transfer giving rise to a successful pregnancy. Ten years ago this was not thought to become preferable to AID or egg donation (Eisenberg 1976), but it may be.

In the laws of most of the countries that permit human embryo research are clauses to prevent research into cloning or parthenogenetic development. Several specifically state that the genotype should not be interfered with. Recommendation

934 of the Council of Europe (1982) covered the application of human genetics and "out of respect for the genetic heritage of mankind" said the genotype should not be interfered with in individuals, "save for clearly and scientifically demonstrated preventive or therapeutic purposes". Recommendation 1100 of the Council of Europe (1989), in accordance with the earlier recommendations, 934 and 1046, permits investigations of viable embryos in vitro only "for applied purposes of a diagnostic nature or for preventive or therapeutic purposes", and "if their non-pathological genetic heritage is not interfered with". Thus, it does leave the opportunity for preimplantation diagnosis, and the possibility for future genetic engineering that cures disease. Genetic research is permitted subject to approval for diagnostic purposes, and also for pre-industrial research if the substances can not be produced in any other way. The recommendations do forbid therapy on the human germinal line, however, they do support somatic cell gene therapy and the insertion of organoids expressing therapeutic genes.

In clinical use of IVF there is the case for some embryo splitting, for diagnosis, and implantation of twins. The rules for embryo experimentation would apply to any embryo, made by any means, by splitting or by some potential embryonic stem cell line. The original goal forseen for cloning was to make copies of some adult, this is not the main pursuit of the cloning we have. The use of cloning to bring in designed genetic change has been accomplished in a limited way using embryonic stem cell lines to make new strains of mice, but it would not seem to be an ethical pursuit if applied to human beings, even if the motivation is honourable. Skills in human embryo manipulation are improving, so in the future it may reach the stage where it presents negligible physical risk to an individual. Therefore, the case has to examined for what problems this will pose to family attitudes, and society's attitudes to the to the child.

The work with ES cells, if conducted within the time and developmental limits for human embryo experimentation, is justified only if we are prepared to justify some human embryo experiments for their scientific or medical benefit. This class of experiments could also be reviewed by the regulatory authorities, in light of the fact that genetic manipulation can yield much scientific information, and the major interest in the roles of genes in development. We could imagine some longterm extrapolation to use for corrective germline gene therapy, however these experiments it could only be justifiable by use of what seems now to be unethical trials, which the first subjects would be. Maybe the work could be progressed on animals to a stage where exact predictability could be reached, in which case there might be some grounds. As discussed, the advantage of using ES cell lines and homologous recombination over the use of retroviruses is the stability of the incorporated genes. If the genes can be manipulated in their natural chromosomal environments, whereas the use of conventional methods for introducing DNA sequences into the germ line allows little control over the chromosomal site of integration and the number of integrated copies.

Human Genome Projects

By mid 1990 we possessed the gene sequences of over 5,000 human genes, and the location of 1,700 genes to areas of specific chromosomes (McKusick 1990).

However, the total number of human genes is thought to be between 50,000 and 100,000. The genome projects aim to sequence all this DNA. Moreover this compromises only 5-10% of the total DNA in the human genome. The rest of the DNA is thought to be nonfunctional. These figures start to give the idea of the size of the projects to obtain a complete sequence of the human genome (a total of about 2.8 billion linear bases on 23 chromosomes).

The Scientific Approach

The scientific methodology for sequencing DNA is routine, but the cost of US$3-5 for each nucleotide must be reduced by a tenth before the major sequencing effort. This should occur as automatic DNA: sequencing methods are improved. The first complete DNA sequences to be determined were of smaller DNA viruses, such as simian virus 40, which contains about 5,000 base pairs, in 1977. By 1982 the tenfold larger sequence of bacteriophage lambda was known, and by 1984 the herpesvirus Epstein-Barr virus sequence of over 100,000 base pairs was known. The total length of human gene sequences that are known today is about 40 million base pairs (Watson 1990). Within the this decade the sequence of the bacterium Escherichia coli should be determined, already 800,000 base pairs of its 4,800,000 base pair genome has been determined. The human genome is still 1,000 times greater than this.

Because over 90% of the DNA is thought to be nonfunctional, some critics have said it is a waste of resources to sequence all the DNA. Critics can call the noncoding information garbage, but as has been said, it is not junk (CIBA 1990), and a better word is to call it non-coding. There are very important functions of noncoding DNA, such as the regions of repeated sequence that are found at the sites of chromosomal organisation, such as telomeres and centromeres. These sites are necessary for organisation of chromosome duplication during reproduction of the DNA sequences that occurs with cell division, and especially for chromosome crossing over during sexual reproduction. Critics would prefer the project to stop after generating a general genetic map of the chromosomes, from which the DNA in which more interesting genes were located, could be isolated and sequenced. The type of mapping, and techniques for identifying a particular disease-causing gene can take several years of intense investigation, as seen in the tracing of the cystic fibrosis gene (Rommens et al. 1989). At least a more detailed map would decrease the amount of DNA that must be searched for each gene. Also, the DNA outside of genes may have some unknown function. It is currently very difficult to tell from a given DNA sequence, whether it is useful or not.

The project is estimated to cost US$ 3 billion over the next 15 years, to the estimated completion in 2005 A.D. (CIBA 1990). The 1991 government funding in the USA specifically for the human genome project (other research is also working on genetic mapping) is US$66 million, but this figure is expected to increase. However, when one compares this with the cost of the development of a single drug, at US$ 50-100 million, or the space station project at over US$15 billion, or the annual U.S. health care expenditure of over US$ 500 billion, it is a small price to pay for such a large amount of information. There are also multi-million dollar projects in Europe and Japan. Every scientist agrees that the mapping part is well worth the investment.

The initial fear of scientists was would the money come from other biological

research or be new money. Within the USA both the Department of Energy and the National Institutes of Health are providing major funding, additional to other biological research (Lewin 1990, Watson 1990).

There are several objectives of genome projects, and there will be benefits as more information is gathered. It requires the establishment and constant improvement of databases containing the sequences of genes, and their location. There are several international databases, and the information should be shared among them (Watts 1990c). The objective is to create an encyclopedia of the human genome, the complete map and sequence. If the information is printed as one character per nucleotide it would require the size of thirteen sets of the Encyclopedia Britannica, without any note of the individual variations in sequence. The data could be stored on half a dozen compact discs. It may be easier to deal in the size of chromosomes, and it was even suggested that each country could be given different chromosomes to work on, to avoid duplication, and to share the costs. The major international effort is centred around the USA, Europe and Japan. There will also need to be technical developments. The actual DNA that will be sequenced will be a composite of different human tissue cell lines, it will not be the DNA of a particular person, but of the species in general.

Coordinated Data-Sharing is Required

The international mapping and sequencing is being coordinated by the Human Genome Organisation (HUGO). Coordination of the international effort is needed, to avoid duplicity of effort which could slow overall progress. The European Commission is also coordinating research in Western Europe. The USA, Japan, U.K., U.S.S.R., and Italy have announced definite programs; France, the E.E.C., Australia and Canada may also join (Watson 1990). There are also needs for the information to be freely shared, though the director of the U.S. National Institutes of Heath Genome Project, Dr. James Watson, earlier threatened that countries that do not contribute funds may not get the information immediately. This remark was targetted at encouraging the Japanese Government to provide funds to HUGO, as well as to their own researchers. However, this has been widely criticised as the information resource belongs to no country, but to the world for its use in medicine. The idea of introducing secrecy would defeat the purposes of coordinating international efforts. The U.K. government is providing £11 million over the next three years, to buy its stake in the use of the information. The idea is that unless they contribute money, governments will lose control of the decisions about how to use the information (Galloway 1990). The most rapid progress will be obtained if data is shared between all researchers. Even if one government declines to support such a project, the information belongs to all people and it is ethical to share it.

There are also private companies embarking on the project (Kanigel 1987), they will be able to patent ways of expressing the genome, though not the genes themselves (see chapter 10). Companies may undertake contracts for research and development with respect to the technical aspects, and they will be necessary, but the final product, the sequence, should not be used for profit (McKusick 1989). Others will be able to obtain the same genes, however it may be cheaper to buy the genes off companies who have found them first. This aspect is controversial, and goes against the idea that genetic information should be freely available. It would be unethical if the information could provide medical therapy if released, as much will

do, so should be discouraged. Perhaps such companies could be rewarded with some funds to reimburse their costs, but it may end up being another case of commercial companies making profits out of human disease. In fact, one commonly voiced aim of the U.S. Genome Project is to promote the U.S. biotechnology industry, as they can sell genetic probes that are made from the gene sequences, and new technology. The political aim is to try to put the U.S. Biotechnology industry above that of other countries, especially Japan. As long as the data is open to all, unless there is a complete change in the economic system, biotechnology companies will make money out of the project. There will be some secrecy, but it is desirable that this is kept to a minimum because other data generators will begin to keep their data secret, and overall progress will be slowed. It will undermine the enthusiasm of scientists to participate in the project if they think that other researchers will hide information.

The problem of data-sharing has always existed, but the advent of biotechnology businesses and the patent possibilities, highlighted this. There are several recent examples. The PCR reaction for DNA amplification was developed by researchers at Cetus Corporation. Although it was given out freely for research work, in 1988 a Cetus official announced that they expected royalties from the commercial extensions and uses of this technique. There was objection to this, and the situation has been clarified, so that Hoffman-Roche is licensed for all diagnostic applications, and researchers who use the PCR machine do not need to pay royalties on discoveries that they make using it. The new technology makes replication of results very rapid, which could encourage researchers to delay publication while they get more of a head start in the next stage of the research. Researchers may not reply to request letters, or just reply within a selected peer group. The U.S. Department of Energy has drafted guidelines that stipulate that data and materials must be made publicly available within 6 months of generation. The NIH is not in favour of rules, but encourages researchers to share information, to avoid bureaucracy (Roberts 1990). The results may be seen soon, as coordinated work on chromosome 21, on which over 30 groups are working, with data-sharing. There is an ethical obligation on researchers, especially those using public money, to share data as soon as it is available. If the scientists cannot do this on their own initiative, which is by far the best option, than regulations need to be looked at. There is much collaborative work, and perhaps the global size of the genome project may reverse the trend, out of necessity, if not for data-sharing ethics.

The knowledge gained should be considered as the common property of humanity. There is an existing legal concept that things which are of international interest of such a scale should become cultural property of all humanity. It can be argued that the genome, being common to all people, is a shared asset, and should be open to all. There is also more public concern regarding the patenting of such genetic material, and it could be excluded as discussed earlier. The debate will continue, as companies will naturally desire to want to obtain some information protection for their investment, but they will have to be sensitive to strong public feelings that could easily be aroused, which as argued, has an ethical backdrop. The idea that the human genome sequence should be public trust and therefore not subjected to copyright was also the conclusion of the National Research Council of the USA (NRC 1988), and by the American Society of Human Genetics. This idea would also include the option that the donor of genetic information, in terms of a cell

line, should be able to make that information publicly available, which is usually a reasonable interpretation of the motives for patients to provide material for medical research, the motive to aid humanity in general rather than a commercial interest.

There have been two major U.S. Reports on this project, one by the Office of Technology Assessment (OTA 1988a), and another by the National Research Council of the National Academy of sciences (NRC 1988). They both recommended that a map of the human genome is made prior to full scale sequencing. While mapping will benefit from improved methods, sequencing requires much improved and cheaper technology. A map is also essential to efficient sequencing so that a library of DNA fragments can be systematically sequenced. We are still in the early stages, and a variety of small scale mapping projects are being supported so that the better methods can be allowed to develop from these. All the data can be made to be interchangeable, by tagging of marker sites by unique DNA sequences, called sequence tag sites (STS) as markers. This will avoid the need to exchange different clones of DNA between laboratories, as each laboratory can use the sequence marker as a starting point (Roberts 1989). The human linkage map is well on the way to completion, the question is how big the gaps between markers should be. The distance used is called a centi-Morgan (cM), and one cM is equivalent to two markers being separated from each other in chromosome crossing over in normal reproduction 1% of the time. The actual physical length of 1cM varies, being approximately 1 million base pairs. The linkage map will be made with an average spacing of 2cM, with maximum gaps of 5cM. The map will of course be improved as the gaps are filled in. Some chromosomes are already covered by markers at 1-5cM intervals. Different research groups have begun to concentrate on different chromosomes in order that they can all have the complete map in a shorter time. The five year goal of the NIH program is construct a map with STS markers spaced at about 100,000 base pairs, and to assemble overlapping contiguous cloned sequences (called contigs) of about 2 million base pair length, of the entire human genome. From this physical and informational library system, the sequencing can be started. Several different methods are being used, as it is uncertain which library-making and marking procedure will be most efficient.

Model organisms are also being studied, and the genomes of other complex systems are being sequenced, such as nematode worms (C. elegans, 100 million base pairs), Drosophila melanogaster (150 million base pairs), mustard (Arabidopsis thaliana, 100 million base pairs) and the mouse. In Japan a rice genome project is commencing. The techniques developed will be transferable between different organisms. Another point is that without comparative sequences we may not be able to understand how the human genome works, how genes are regulated in a coordinated way during the lifetime of an organism. The initial target is the development of new technology. Data management technology must also improve, such as programmes to search the DNA sequence libraries, using advanced computing technology.

There had been talk of giving different countries the tasks of sequencing different chromosomes to avoid duplication, however such as system was considered impractical given the way scientists work. Also most chromosomes have already some preliminary map. There are actually 24 different chromosomes that need to be sequenced, the 22 autosomes and the X and the Y chromosomes. Many researchers remain more interested in pursuing specific disease-causing

genes. There are only a few chromosomes that are being extensively mapped at the moment, these include chromosome 21, which is small and contains the Alzheimer's susceptability; chromosome 7, and chromosome X. Other chromosomes, such as number 8, which have few known genetic diseases linked to it, are poorly known. The coordinators, in this way HUGO plays a useful role, can point out the number of existing projects on each chromosome to those who submit research proposals mapping such chromosomes. National medical research funding bodies can possibly reject funding applications that are overlapping. To duplicate work is important for confirmation, but certain areas may have a dozen teams working at the same goal which is a waste of effort.

Ethical Implications

There are major applications and implications of such work. It will be a huge resource of information for medicine in the next century. There will be much useful information arising prior to the completion of the project, as many disease causing genes are sequenced and the mutations characterised. There have been many potential ethical and legal problems raised (CIBA 1990), especially from the scale of the information (Friedmann 1990a). The possibility of mastery and control over the human DNA raises the issue of genetic selection (OTA 1988a). It would be possible to develop DNA probes to diagnose any known genetic disorder, and also would be easier to characterise new disorders. This is important for genetic screening, and therapy of diseases as currently most disease causing genes have not been identified or located. The gene responsible for each genetic disease will be isolated. It will also be possible to expand the number of human proteins that can be made by genetically-modified organisms, which would allow conventional symptomatic therapy for many more diseases, which could be supplemented by somatic cell gene therapy when appropriate. It would also expand our basic knowledge of human biology, which allows medical treatments to be developed. It is obvious that within the next few decades medicine will undergo a major change, this is the beneficial side of the extra knowledge. The amount of new knowledge is hard for us to comprehend, it will take decades to process it all, but it offers the potential understanding of all genetic diseases sometime during the next century. We should remember that understanding the genetic mutation that causes a disease is very different to being able to treat it, for example it has been thirty years since we knew the mutation that causes sickle cell disease, but we are still developing effective therapies.

We must also be aware that this new knowledge, which we must accept will be known probably within fifteen years, will allow ideas of eugenics to be explored. We need to maintain a distinction between diagnosis and treatment of disease, and selection for desirability. This fear has lead to calls for research into the social and ethical implications of this research. The techniques that we possess now, and will possess in the next twenty years are much more powerful then the techniques used early this century. We will get some idea of the possibilities by looking at the animals that can be made using the new genetic techniques in the next few years.

The ethical debate must focus on how to use the new information, rather than on whether to discover it. Most religious approaches support the rationale for obtaining better genetic information, which can be used to alleviate human suffering (Kimura 1990). The decisions to progress, have already been made, and there are

certainly many benefits from the project. The question of fairness in the use of genetic information with respect to insurance, employment, criminal law, adoptions, the educational system and other areas must be addressed. The impact of the information on the individual is a different perspective. We must avoid stigmatisation or ostracism, and labelling in general, and look at the individual psychological responses. The ownership and control of genetic information, and the consent to use such information must be addressed. There will need to be more serious consideration given to personal reproductive decisions in the future, making life more complicated while hopefully improving its quality. Some of these issues have been discussed in former sections of this book, and obviously more attention is needed. We should note that the amount of information obtained will overwhelm existing genetics services, and geneticists. More training of genetics (as well as ethics) will be required for physicians and health care workers.

The time is right for much discussion regarding how we use the information. It is proposed that in the USA from 1991, town meetings may be held to inform the general public about the human genome initiative, and to solicit opinions on the ethical, social and legal issues that it raises. The human genome project has even found its way into French school books, and it is important for such widespread education to be available in a way that the public can understand it. An adequately prepared lay community is the best way to ensure that misuse of genetics does not reoccur. There should also be education to show that despite all the information, we should not expect disease to be cured within twenty years, and it will not be a panacea for the world's woes.

It is pointless to bury our heads in the sand, as the knowledge will come. The question is how to use it for proper stewardship. There are dangers in any large scientific projects, that they take control of the people, in becoming the sole ideal for progress. We have seen this in the past with the Manhattan project, and the Apollo project. From the initial response to the human genome project, this is also happening here (Annas 1989).

The topics addressed in last three chapters, and this one, on the use of genetic information are the applied use of this information. The Human Genome Project itself will succeed, in the absence of any wider catastrophe. We need to solve some of the existing dilemmas before the information is overwhelming. Rather than delaying the research, it means we must no longer delay public discussion of the issues. Long term health plans must be devised with this in mind. For example, the recent U.S. Presidential Office Health Care plans until the year 2,000 do not include the establishment of coordinated genetic screening services for prenatal diagnosis, let alone incorporating them into a National Health Service. These developments are not only desirable, but inevitable, and the sooner governments realise this the less problems will have accumulated when the time comes to switch to national health schemes. The injustice of private health care schemes will be accentuated. Like it or not, ethics in terms of justice may become a political issue in some countries.

Fears of Genetic Determinism

There will be a change in attitude to ourselves also, and genetic determinism might become popular, the idea that the answer to our problems lies in the genes. Determinism is the idea that there are causal mechanisms for any action. By tracing the pathways between genes and behaviour we may start to get a determinist picture.

Already some genetic work in psychiatry can aid that picture, which has only limited truth. For instance the pattern of behaviour classified by psychiatrists as sensation seeking, involves a disposition to gambling and drinking, and can be correlated with low levels of activity of an enzyme platelet monoaminase oxidase. Of course there may not be any causal relationship, but people seeking an explanation or not totally informed, can easily jump to conclusions. A danger with simple-minded adherence to genetic hypotheses for behaviour is that it oversimplifies the complex interaction of genetics and environment. There may also be elements of homosexual behaviour that cause predisposition to it from childhood experience or genes, this could lead to labelling of such people and the belief that such behaviour is unpreventable. In the extreme determinism eliminates the idea of genuine choice, leaving no room for the belief that we can create, or modify ourselves, or that we can make moral choices. What people should already have seen from the genetic knowledge that we have, is that most behaviour does not follow patterns in our genes, as we can change in our lives very much. It is thought that perhaps a third of the genes are brain-specific genes, maybe more, and the genome project promises much for that area also. The question whether higher human attributes are reducible to molecular sequences is a controversy in philosophy of biology

The knowledge of human genetics will make scientific understanding of human life much more sophisticated. We may be able to understand the degree to which genetic factors control behaviour. If the information reveals that individuals have less options for variance then they suppose, then a determinist view will emerge. There may be alteration in social customs, especially if the information is misunderstood by the public as occured at the beginning of this century. For instance your gene profile might say that you can only do an undergraduate degree in history, and discourage you from doing anything more difficult, or from anything easier. However, our genes are not that deterministic, we only have to look at the variety of people in different social clubs. In many cases, changing social policy and encouraging individuals to alter behaviour will be a better remedy than using genetics.

Our Future Obligations

The other side of the argument, is whether society will allow individuals to have free choice over the use of genetic manipulation when there is no medical reason for it. Society already prevents attempts at medical therapy if there are possible risks, in the controlling of the use of somatic cell gene therapy. In the case of somatic cell therapy, an existing individual with a problem exists, which involves some healing obligation to cure. In the case of germ-line manipulation however, there is no existing individual, but unless the therapy is performed (assuming the parents reject the use of donor gametes or child adoption), there will be an individual with a problem. In the case of many diseases, it is best if the gene defect is fixed before it has a chance to damage the fetus/child's development.

There are various arguments used against genetic intervention which has no therapeutic value, and some of these have been already outlined. It would be a waste of resources, may present risks to offspring, it will promote a bad family attitude, will be harmful support of society's prejudices and may reduce social

variability. It will probably not have any significant affect on genetic variability as there will be plenty of alternative healthy alleles. There could also be the idea of a natural genetic autonomy, that we should let the genes come together naturally, and let the individuals develop their genetic potential without unnecessary interference by parents or society. While we can justify the curing of disease, we can not justify enhancement engineering. A criteria for transgenerational ethics is that not only must a gene alteration be safe, but it must be good therapeutic sense in many generations. There must be unquestionable objectives and benefits, for many generations.

A common feature of these issues is that we need to consider the effects of technology on future generations. We have a responsibility to future generations. The beneficiaries and those at risk may not yet be existing. We have an obligation to the future (Rawls 1971, Blank 1984). The human genome project raises some similar ethical and legal issues to those in current genetic screening, such as confidentiality of the results. However, it will lead to screening on a huge scale, for many disease traits and susceptability to disease. It is important that we deal satisfactorily with the test cases, before we are faced with all these new information. The technology may change the way we think.

Our traditional view of morality only involves short term consequences. Human action is seen as only having a small effective action range. Moral liability is limited by what is unenforcible. If another agent intervenes, or something unexpected happens, it is not considered our fault. Genetic engineering changes our moral horizon. For that we should be very grateful, as for too long we only examined short range effects.

We can see similar problems emerging with the environmental crisis. In this way discussion of germline genetic engineering contributes to our ethical thinking. The ethics of long range responsibility are needed. It implies that there is a moral imperative to obtain predictive knowledge and data about the wide-ranging possibilities of some action. Secondary consequences may be sufficient to prevent the primary action, even when the primary action may be good. This imposes a restraint on the use of technology. In this respect this ethics is important for public policy decisions, beyond the physicians concerns with each patient, or the scientists concerns with increasing yield of some crop variety.

It means that researchers may be held accountable for secondary consequences of their research. Of course it may be very difficult to predict what will happen in the future, the social pressures and thinking are already very distinct between different countries. If social ideas change, then so may the pressures, such as the desire to use genetic enhancement. We need to ensure future generations retain the same power over their destiny as we do, while benefiting from the culture and technology we have developed.

16. Bioethics for the Future

During the discussion of the advances in new genetic and reproductive technologies and the ethical problems that arise, we can see how some basic principles of ethics can be applied. These are not only useful in making decisions but may be necessary to the successful use of this technology. The new technologies do not create many new ethical problems, except for the focus on future generations, but they certainly magnify preexisiting problems. This magnification will be most apparent during the next two decades as we obtain so much basic genetic information, and the techniques utilising this are fine tuned.

Medical Ethics and Genethics

Now we can summarise how the principles that are found in the Hippocratic tradition, and in other approaches to medical ethics, stand up to the challenges of new technology. We can also see what the implications of genetics are for changing our ethics. I will start by a consideration of the profession, which while not being an ethical consideration, is perhaps the most dominant feature of the Hippocratic:tradition that characterises physicians. It is also being adopted by other health care workers, along with their own similar ethical codes.

Professionalism

At the heart of modern medicine is the concept of a profession. There are several ways to view medicine, it can be viewed as an art common to Hippocratic language, or it can be viewed as a science, a vocation, a service and as a profession. The word profession originally comes from a theological source, for a public declaration of promises or vows which was made by a person on entering the discipline of a religious order. It became secularised, like the word, vocation, in the sixteenth century, and was first used in reference to the medical profession, then also applied to lawyers, clergy and military officers (Wilkinson 1988). It is now the most common word to refer to medicine. In Ancient Greece medicine was considered not only as an art, but more generally as a livelihood, something in common with today. The attitude of Greek society to the physician was based on this idea, as the physician competed for patients to obtain financial gain. Today there is much more security in being a physician, and it is viewed by many as a gateway for a good life. The average earnings of a physician in general practice in Japan are seven times that of the average person, and rising. For the physicians in clinics, this figure may be double. This inequality in wealth is also true of many other countries. Professionalism provides much of the ideal framework for medicine according to many within it.

A profession could be defined as an occupation that involves mastery of a systematic body of knowledge and requires dedication to an ideal of service to others. At the core of professionalism is the acceptance of fees for services, the use of technical terminology, the wearing of profession symbols, the passing of formal training requirements, and licensing, a monopoly, the autonomy of the profession and higher social status (Unschuld 1979). Most professions are parties to a social contract with ethical overtones. The ideology of a profession provides practitioners with a set of behavioural standards to help resolve conflicts, which involves making a set of professional ethics (Pernick 1978). Most professions claim final authority for defining their own standards, though these change over time (Berlant 1975). Today, specialisation is the trend, but last century that would of been quackery (Shryock 1967). Many modern critics believe that professionalism must give way to reform (Illich 1975).

The physician's development of a formulated ethics needs to be understood from the perspective of the peculiar nature of the resources in question. In favourable situations, the physician and the patient benefit; but in the unfavourable case there can be fatal consequences; in some ancient cultures it could be fatal for both. There was the widespread suspicion that death or injury of a patient might be premeditated by the physician. In cases of success, the physicians were rewarded, but in the case of failure they were forced to protect themselves; though today they are rewarded even if they fail to cure the patient. A necessity to protect themselves has been a major concern. Unschuld (1979) sketches three major mechanisms of protection. The responsibility for the outcome of individual cases has often been denied, and the results viewed as the outcome of supernatural powers, often putting the blame on the patient's sin. Prognosis was developed, which had two major functions. It can help to build up a good name if impressive forecasts of the outcome of disease can be made; and it has a protective function of separating the curable patients from the incurable. The ancient physician could accept profitable cases only. The third mechanism is to develop a formulated ethical code, such as the Hippocratic Oath, was seen in various cultures. It is better than prognosis as all patients can be "treated". It diverts the attention of the public from the outcome of medical activity to the process. The public is persuaded to believe that physicians who follow the code will be trustworthy. Any negative results are viewed as acts of God, or nature, beyond man's control. Formal medical ethics developed not so much from philosophical roots, but were guided by sociological principles shared with guild formation (King 1958).

There are three sources of guidance for professional conduct, the rules of etiquette between members of the profession, the codes of conduct to regulate the relationships between members of the profession and the general public, and any philosophical and religious beliefs underlying professional conduct. An example of etiquette is to call the physician "doctor" even though they do not hold a university doctorate, which dates from the thirteenth century at Salerno medical school.

In Britain the Royal College of Physicians (RCP) functioned to restrict the practise of medicine. The RCP was a guild in constant competition with the apothecaries guild, and this led to codes of medical ethics. In the seventeenth century there were not enough physicians, so apothecaries were needed. The RCP tried to follow their charter to protect the public, but it did not raise standards. In 1704 the House of Lords allowed apothecaries a new status. Also the previous

educational situation changed from being solely the realm of Oxbridge, as Scottish Universities had better medical schools. The distinction maintained between Oxbridge fellows of the RCP and non-voting licentiates led to much trouble. This was the background for the elaboration of codes of medical ethics. In America restrictive licensing only became universal after the establishment of federal associations such as the American Medical Association (AMA) and the New York Academy of Medicine with their codes of ethics. Statutory legislation was later introduced by many governments, in accord with medical association codes. A precondition for the development of professional ethics was the breakdown of the patronage system, there must have been a desire for colleague control. In the eighteenth century control was by patronage, or client control. The aristocratic and wealthy client was the dominant partner in the physician-patient relationship. The physician identifies with his patron, rather than professional colleagues, so that there is little group solidarity (Waddington 1975).

We can see the thinking behind the development of medical ethical codes by reading works such as *Percival's Medical Ethics* (1803). Among Percival's section on general practice is advice in trust-building, to build up the trust of the public. These devices aid the process of monopolisation. Trust inducement increases the market value of medical services and helps convert them into commodities. It flatters the doctors, helping their integration into a professional group. It also maintains the paternalistic relationship. The patient is persuaded that they do not need to protect their own interests. The paternalism results in the profession dealing with fragmented individuals, who themselves want to be on good terms with the doctors. Trust inducement also legitimises licensing privileges, as only the fellow physicians are able to judge (Berlant 1975). Other measures can also be seen to increase monopolisation, such as the rules for consultation which encourage group solidarity rather than competition, and for the transfer of patients between different doctors, and many directives to avoid criticism of other physicians which would undermine the profession, or the building of the monopoly. The 1847 AMA Code states that the care for the sick constitutes an obligation "the more deep and enduring, because there is no tribunal, other than his own conscience to adjudge penalties for carelessness or neglect". The AMA Code said that the subject matter of differences should not even be made public, reducing the probability of public criticism and consumer organisation. This is bourn out up to the present day, where very rarely is action ever taken for malpractice. Percival was opposed to any form of competition. This is not explicit in the Hippocratic Oath, as it was practising in quite a different situation, however, it could be said to be part of the Hippocratic tradition. Percival's code shares some features with the RCP London statues of 1543-1563 regarding physician's behaviour (Clark 1963). John Gregory's system was very different, attacking monopolistic medical corporations. He challenged the ideas of common medical training and support of each physician as being the best ways of building up the professionality and excellence of medicine. He criticised the formalism and restriction of knowledge within the profession (Berlant 1975). He also criticised the self-regulating body of elitist experts, saying that confining practice "entirely to a class of men who live by it as a profession, is unfavourable to the progress of the art" (Gregory 1772).

The medical profession in the United States was aided by the rise of science, as the profession obtained much more authority. Scientific expertise was defined as

the primary professional qualification in medicine (Flexner 1910), and by the 1930's the number of medical schools had dropped significantly so that virtually all of them were following the Flexner curriculum (Pernick 1978). After the war the American Medical Association was powerful enough to defeat plans for a federal health insurance scheme (Burrow 1978). Development of a professional ethics was important in the professionalisation of medicine in China also (Unschuld 1979).

Some physicians ground their ethical obligations in a pledge and group loyalty, claiming that physicians are a privileged group given high rank and they have a special duty to promote the welfare of others (Ballantine 1979). They even claim that society has bestowed this special status on their profession. A code of professional ethics needs to be accessible to the general population, as it applies to them. The Hippocratic Oath contains a pledge of professional secrecy, which is certainly also found in the medical profession today. They attempt, at least in some countries, to close the discussion of medical ethics to within the profession. The pledges or promises made by the medical profession are not necessarily those desired outside of the professional group. It must be an interesting story why the *Hippocratic Oath in-so-far as a Christian may Swear It,* was not accepted. For the purposes of comparison I give this oath below (Jones 1924):

Blessed be God the Father of our Lord Jesus Christ, who is blessed for ever and ever; I lie not.
I will bring no stain upon the learning of the medical art. Neither will I give poison to anybody though asked to do so, nor will I suggest such a plan. Similarly I will not give treatment to women to cause abortion, treatment neither from above nor from below. But I will teach this art, to those who require to learn it, without grudging and without an indenture. I will use treatment to help the sick according to my ability and judgment. And in purity and in holiness I will guard my art. Into whatsoever houses I enter, I will do so to help the sick, keeping myself free from all wrongdoing, intentional or unintentional, tending to death or to injury, and from fornication with bond or free, man or woman. Whatsoever in the course of practice I see or hear (or outside my practice in social intercourse) that ought not to be published abroad, I will not divulge, but consider such things to be holy secrets. Now if I keep this oath and break it not, may God be my helper in my life and art, and may I be honoured among all men for all time. If I keep faith, well, but If I forswear myself may the opposite befall me.

The original version of the Hippocratic Oath is on page 46 (chapter 4). The unknown authors of this Oath have deleted the pledge of secrecy found in the original oath. Also deleted are the parts which talk of a brotherly club. It could be that the interests of guild formation lead to a preference for the original.

Demands for a professional oath do not seem to be compelling, as there is no known medical system capable of solving all health problems. Only if we seek to retain the dominance of medicine and the current medical paradigm, then a code is desired. There does need to be some system of medical law, but it is a very different thing to require physicians to swear it. In fact in Britain only one medical school apparently asks graduates to swear the Oath (Orr 1988). Virtually all of the professional codes, in contrast with the public codes, devote much attention to relationships between members of the profession. The longest section of the 1847 American Medical Association code was "the duties of physicians to each other and to the profession at large". The ethics of a profession are defended on several grounds. On "universal" grounds, that the public should accept that the profession is

closed and regulated for the public good. On the grounds that it is a special profession and nonmembers should not be expected to share in the fraternal loyalty of a special group. There is also the idea that medicine is the most pure of the professions and the ethic of dignity and that of gentleman should govern the brotherhood. In the 1980 AMA statement on the principles of medical ethics there is more recognition of the duties to other people. It states, "As a member of this profession, a physician must recognise responsibility not only to patients, but also to society, to other medical professions, and to self." It goes on to say that a physician shall "strive to expose those physicians deficient in character or competence, or who engage in fraud or deception."

The profession can even judge cases in law of professional misconduct, which is different to the professions own speciality. Peer review of problems is encouraged before this stage, however, professional monitoring of members misconduct is a problem as the members will try to protect the profession as a whole (Veatch 1981). An ethic articulated by physicians only handles a small fraction of the ethical problems in medicine. Certainly, if a physician has been unethical it could be said that he no longer should be regarded as a brother, and should be exposed (Orr 1988), but very often this is not the result. On the otherhand, a sytem of confrontational medical malpractice, as seen in the USA, can be worse. It results in high medical costs when associated with unlimited viability, and erodes the trust between patient and health workers.

This narrow view of the medical profession is changing in some places. What we see from the use of new birth technologies and genetic counseling particularly, is that there needs to be many people involved in the process of aiding patients decisions and coping with the consequences of them. The knowledge that used to be restricted to the physicians is more widely available, though they should by virtue of their training retain more specialist knowledge. The days of a narrow medical profession who can claim only they are aware of the problems and make choices for patients is gone. However, many do not want to recognise that. These techniques require the cooperation of physicians with nurses, scientists, psychologists, counsellors, and families of the patients in a coordinated way, beyond the patient relationship. In almost all parts of this book that considered ethical dilemmas, the word physician could be substituted by the broader term, health care worker. I hope that nonphysicians will excuse my continued use of the term physician. This is the way that is suggested by some recent writers and the need is especially highlighted by the use of new genetic and reproductive techniques.

What Ethical Principles?

The directive of the Hippocratic Oath to benefit the patient according to the physician's ability and judgement, is no longer regarded by medical ethicists' as the principle guiding principle for medical ethics. It can not be left up to the physician's prerogative or the elements of the Hippocratic tradition. There is paternalism implicit in the Oath's instructions that the physician may refuse his patients' requests in some cases, such as refusing requests for abortions or poisons, and to judge what confidences to keep. The instructions of Percival (1803) to doctors ends with "They

should study, also, in their department, so as to unite tenderness with firmness, and condescension with authority, as to inspire the minds of their patients with gratitude, respect and confidence". It appears that it has long been assumed that paternalism and professional status wins the confidence of patients. There is no notion of consent in this tradition. In actual practice, the physician is influenced by many factors. Above all, is to benefit individual patients, in accordance with the most objective judgement available, legally being that approved by the consensus of the medical profession, but most importantly according to the patient's own judgement. Recognition of informed consent is not always going to lead to the most beneficial outcome for the patient, but it is the price of demcracy. We must accept people's autonomy, their own desires, as the most important principle for medical ethics. This means that the fundamental principle of the Hippocratic tradition has changed, and we must question the continued recourse to the tradition as one which expounds our system of medical ethics.

After a brief discussion of the context and validity of the concerns regarding new genetic technologies, we need to ask what are the key principles that are needed, and are these any different to ones governing behaviour already. The moral problems of genetics are not inherent in the process itself, but contingent upon their use.

We must view medicine in terms of families and society. The implications of individual patient decisions are far wider then they used to be, as the power given by technology is greater. The human side of therapy is not the speciality of the medical profession, but it should be. The selection process for medical students in most countries pays very little attention to the ability for human interaction, rather selecting out those that can obtain highest marks in an academic examination system, together with family wealth and profession, and connections. The counseling ability of physicians is probably only average, unless it is trained. Trained counselors are essential for the new techniques. With the introduction of computer-based prognosis methods there is less need to concentrate on the academic selection, and it may be a good time to try to introduce more human factors.

In the decision making of medical ethics a multidisciplinary approach is desired. However, this requires an openness of physicians to allow others to advise and enter their decision making. There are still physicians to be heard that say that only physicians should be involved in making ethical decisions with patients (Sullivan 1990). Perhaps they feel their authority threatened, as people enter from outside the closed-doors of their profession. We must work to remove this elitism. The contrast between different countries is also very great. Hopefully after the transition period of another decade or two more common approaches that respect ethical principles are in place. Medical schools not only need to teach medical ethics, but to work on opening the attitudes of the next generation of physicians so they can accept the advise of others.

Policy making is a broader level, and is even more multidisciplinary. Questions such as whether health care is a basic human right, like education, have been officially decided in nearly all countries. However, the systems in use may not allow access to all people. The groups of different interests and specialities need to be represented and listen to each other. Some of these policies may involve limiting choices that the medical profession may make, such as laws on abortion, euthanasia, or reproductive technology. This conflict has occured, and will continue to, and

less power will be in hands of the medical profession. We should hope that rather than this power moving into the hands of some new group, or politicians, that it is shared to represent the interests of democratic societies.

Part of the Hippocratic tradition is that the practice of the physician's Art is a calling, like a religious vocation. Despite the inadequacy of the Oath, it is still the most often-cited summary of the physician's own understanding of what is normally required to be a good medical doctor. However it must change; the obligations are stated as absolutes without any reference to patient values. Today's complex decisions need to include patient values which can vary widely, not just between different religious and cultural groups. The patient's values must be respected whenever possible and whenever they do not create an injustice for others (Pellegrino 1987). The tradition focuses on the outcomes, it is consequentialist, like a utilitarian ethic, however, the physician can not judge the economic, spiritual and other nonmedical dimensions of benefit to the patient beyond physical health. There needs to be some way of assessing these, which is not present in the Oath.

There are many new technological innovations, and the potential to manipulate the human body, personality and life itself. Death and conception can be altered, which means some new issues are present. The Oath comments on euthanasia but it does not consider maintaining human life in some sort of vegetable state, or the survival of severely handicapped newborns after major operations. It prohibits abortion, but it does not consider the situation of prenatal genetic screening.

The professional's judgement about what is required does not decide ethical issues. For instance some ethical decisions may be extremely private, such as suicide. Usually there should be a private agreement between the medic and the patient to pursue what is the patient's best interests. Overall there must be an ethic fair to all, and there have been various attempts at defining principles of medical ethics (Veatch 1981, Engelhardt 1984, Brody 1988, Beauchamp & Childress 1989). In a simpler world, the Hippocratic ethics which has long sufficed to guide physicians in their service to patients and the community would remain useful, but today with the intersections of medicine with contemporary science, technology, and the different social organisation and changed human values, there are significant missing dimensions in the Hippocratic ethic (Pellegrino 1987). Having argued that the first part of the Hippocratic Oath is out moded and needs to change, let us consider the ethical principles that we need to use.

Beneficience

One of the underlying philosophical ideas of society is to pursue progress. The most cited justification for this is the pursuit of improved medicines and health. It has often been assumed that it is better to attempt to do good than to try not to do harm (Callahan 1979, Beauchamp & Childress 1989). A failure to attempt to do good, working for the patient's best interests, is taken to be a form of doing harm, a sin of omission. This is the principle of beneficience. This is a powerful impetus for further research into ways of improving health and agriculture.

The term beneficience suggests more than actions of mercy, for which charity would be a better term. The principle of beneficience asserts an obligation to help others further their important and legitimate interests (Beauchamp & Childress 1989). It also includes the weighing of risks, to avoid doing harm. While we may pursue techniques to make genetic screening possible, it may not always be in the

best interests of the patient to use the tests. Genetic screening requires many decisions like this, and in a few cases beneficience is more important than autonomy.

Respect for Human Life and Autonomy

This is a very broad term, but is the basis for the principles of justice and confidentiality, and philantropy. It can also be expressed as "do no harm". The reason we do no harm is because we respect human life. This feature is found in the Hippocratic tradition and all other traditions of medical ethics. It is expressed more at an individual level, whereas justice is the expression of this concept at a societal level. This idea has been called the principle of nonmalefience. Those who claim the individual autonomy comes above societal interests need to remember that at major part of protecting society is because it involves many human lives, which must be respected.

Abortion and euthanasia are practised today, but they were also practised at the time of the Oath. They remain controversial. It is still a matter of intense debate how stringent the criteria must be, there will be exceptions to absolute prohibitions, much more reasoned argument is needed beyond the citing of the Hippocratic Oath to forbid them. The Oath does highlight these two constant areas of medical concern, that have remained so for 2,500 years.

We need much more refinement and guidelines when it comes to these questions. The feature that is emerging from modern thinking is to think in terms of human persons, both their birth and death. Respect for human persons is a more precise wording of this concept, and may clarify issues such as abortion or euthanasia.

Justice

Medicine until very recently, has lacked any full theory of justice or the duty of physicians to treat those in need, this is in contrast to many religious views which compel physicians to actively seek out the sick. Some of the major proscriptions of the Hippocratic Oath are already compromised - confidentiality can be violated under certain conditions of law and public safety, abortion has been legalised, dangerous drugs used everywhere, some human experimentation permitted, and euthanasia has been made legal in some countries.

The Hippocratic ethic is individualistic, very different to the approach of classical utilitarian ethics. Physicians still seem to maintain that the physician has a special ethical obligation to benefit the patient, independently of the net consequences for others who are nonpatients. In 1957 the American Medical Association instructed physicians that "the principle objective of the medical profession is to render service to humanity, not the individual patient", an idea also found in the current Soviet physician's Oath. We cannot be individualistic, the sick must not mean the individual only, but the plural. Public health questions are important, as is medical experimentation. Some public health decisions such as vaccination programs actually involve a small risk of fatality to the individual, which is judged to be offset by the reduction in deaths by the disease in the society as a whole. Justice and some egalitarian ideal are absent from the Oath, as the physician under the Hippocratic Oath could chose which patients to accept. Charitable medical

care is an ethical duty without Hippocratic roots, but is a worthy ideal. However,with the runaway costs of modern medicine there will be times when individual patients can not be treated unless broader health policy is improved. The principle of justice will be essential in the next century because people can be genetically screened, and this information can reveal much sensitive information that can influence life choices for that person. We must seek a just health care system, so that all people can be fairly treated, despite our inadequacies and differences.

The key principle arising from the high value of human life is respect for autonomy of each individual human being. This means they should have the freedom to decide major issues regarding their life, and is behind the idea of human rights. This idea is found in many religions also. Part of autonomy is some freedom to decide what to do, as long as it does not harm others, also called individual liberty or privacy. Well-being includes the principle of "do no harm" to the patient, and to work for the patient's best interests.

The autonomy is limited by respect for the autonomy of other individuals in the society. People's well-being should be promoted, and their values and choice respected, but equally, which places limits on the pursuit of individual autonomy. Society should also include the future of society, future generations are also an essential part of society.

Confidentiality

The emphasis on confidentiality as outlined in the Hippocratic Oath gains much support. The keeping of confidences is necessary to retain the patient's trust, and has been a common feature of medical ethics since. However, today the codes usually include the exception in the cases of criminal activity. It is very difficult to develop a good referral criterion for exceptions, and they will remain rare (Carrick 1985).

A feature of the ethical use of new genetics is the privacy of genetic information. This is one of the residual features of the Hippocratic tradition that needs to be maintained. It is not only because of respect for peoples autonomy, if that is not enough. It is also needed to retain trust with people. If we break a person's confidences, than we can not be trusted. It applies to all aspects of life. We need to protect individuals from discrimination that may come in an imperfect world, one that does not hold justice as its pinacle.

There may need to be exceptions if other people are directly at risk from not knowing the condition of a patient. However, in the case of a predisposition for a certain illness, or the case of the inevitable development of a illness, the informed individual should have the right to keep this information that will affect their future life. Only when symptoms show that will affect a third party should their condition be reported if they have not already voluntary done so. There must be care in the reporting also, so that it is not widely spread. We must be careful, because we use computer databanks that contain such information, and if they can not be kept confidential, the information should not be entered to such a bank.

An extension of confidentiality is privacy, the right to refuse questions. If medical insurance companies try to take only low risk clients by presreening the applicants, their should be the right to refuse such questions. The only way to ensure proper and just health care is to enforce this on insurance companies, or what is a better solution, a national health care system allowing all access to free medical

treatment.

Proportionality

As has been apparent throughout this book, there needs to be a balancing of conflicting principles of ethics. Different people's interests will conflict, so that there are exceptions to the maintenance of privacy, confidentiality. How do we balance protecting one person's autonomy with the principle of justice, that is protecting all people's autonomy. In this regard utilitarianism will aways have some place, though it is very difficult to assign values to different people's interests and preferences.

Genetic engineering is challenging because it is a technology with which both benefits and risks are associated, and will aways be associated. Human beings are challenged to make ethical decisions, they have to. The benefits are great, but there are many possible risks. Although our life may have become easy, so that we avoid making very many decisions, we must. The more possibilities that we have, the more decisions that we make. Fortunately standards of education are increasing, but this is no guarantee that the right decisions will be made. People need to be taught more on how to make decisions, and the education system should accommodate this need of modern life.

Legislation or Consultation

The law has become very important in many aspects of life. The function of the law is to protect the individual autonomy of people so that they can have some freedom, while protecting the rest of society if they abuse that freedom. In the area of the use of new genetic technology the law has been challenged by rapid advances, that very few had foreseen, so it is predictable the law is lagging behind. In the rush to introduce laws, we must remember that technology continues to change, and we must be cautious that our laws allow for changing science, but also that they allow us to use technology when it is ethical to do so.

The law faces problems, should it be inflexible, in the form of rules to follow, that may soon be outdated, or should it be subject to challenge in the courts, so that case law can guide. There are several different views of the law, and these could be called the formal, the substantive and the reflexive (Jabbari 1990). An example of formal law, is the fixed law of contract, it generates fixed rules which would not be overcome even in the event of injustice. Certain classes of transactions have been outlawed, such as baby exchange in surrogate mother contracts, which are not recognised in many countries. Formal law is aimed at intervening in a process to obtain a clear result. Critics of this approach have been common when considering the medical issues, and they suggest that we should use a reflexive approach, that can change with the times. It aims to create procedures, like formal law, but procedures that would govern the way discussion occurs and decisions are made.

For the purposes of regulation of science, reflexive law involves the establishment of committees that can make decisions. The decisions in the best case can be made unanimously, after receiving expert advice. For instance the decision might be whether a procedure to use a human embryo for a certain experiment is ethical. It might be to consider the release for field trials of a new GMO. The emphasis is on self-regulation, or regulation by a specialist committee that is used to

making that sort of decision (the members of whom should be interdisciplinary). In the recent British Human Embryology and Fertilisation Act, a Statutory Licensing Authority was established to regulate the clinics that perform IVF, and also to regulate human embryo experiments up to a limit of 14 days (HMG 1990). This is in the spirit of a reflexive law, however there were also some formal parts of the legislation, such that genetic manipulation of the embryo is criminalised, as is trans-species fertilisation (Jabbari 1990). In the few countries that are yet to introduce formal legislation, it will be interesting if they can trust such committees to make more decisions. It is appropriate if the committee is well defined, but it may take a while for lawmakers to change.

There have been bioethics committees established in some countries, with good success. There is a National Bioethics Consultative Council in Australia, which has been working well for two years. There has been a French National Bioethics Committee for 7 years, though it has 37 members, which may be too many for what is required. There is a National Ethics Council in Denmark, which is now working well after initial controversy. The President's Commission in the USA was very successful, between 1980 and 1983, but was disbanded. There is a Bioethics Committee in the Council of Europe, though it only considers medical issues. There are signs that people are realising that the nature of the technological advances is such that a flexible approach to regulation is the best in many cases.

Universal Approaches

In many developed countries it is apparent when you walk in the street, or read the newspaper, that the country is mixed. Ever more than before, universally applicable ethical principles are necessary. Many immigrants have come to North America, and to the old European Empires. The practises that immigrants are accustomed to differs from each other. Their religions are different, and cultures. In medicine, the patient-physician relationship is critically determined by these differences.

The Declaration of Geneva (WMA 1948) was amended by the WMA in 1983. They suggest an Oath that physicians could take upon graduation. I present it below for comment (WMA 1983):

At the time of being admitted as a member of the medical profession:
I solemnly pledge myself to consecrate my life to the service of humanity;
I will give to my teachers the respect and gratitude which is their due;
I will practice my profession with conscience and dignity;
The health of my patient will be my first consideration;
I will respect the secrets which are confided in me, even after the patient has died;
I will maintain by all the means in my power, the honor and the noble traditions of the medical profession;
My colleagues will be my brothers;
I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient;
I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity.
I make these promises solemnly, freely, and upon my honor.

It retains much of the brotherly professional wording of the Hippocratic tradition. It is very individualistic, though given the efforts required to introduce informed

consent in many countries, this neglect of society"s interests may be justified. It includes a useful sentence in this respect, not to let religious, nationalistic, racial, political or social influences influence the duty to the patient. While we need to consider societal interests because of justice, we must establish a value sytem in medical practice which recognises the autonomy of persons.

A country can impose laws, or screening policies, but the real focus needs to be on the point at which the public interacts with the system, the health care providers. There may be differences of language to further complicate the cultural difference. The human approach to this relationship is especially stressed in the difficult dilemmas faced in genetic counseling. Similar issues are in the rest of medicine. What we must do is apply the emphasis of genetic counseling on nondirective counseling back into the rest of medicine. To respect people's autonomy and obtained truly informed consent is required. In this way we can learn from the new genetics.

There are important duties on health care providers. They should be advocates for their patients, and attempt to ensure that society in general makes adequate provision for the needs of patients. The distribution of wealth needs to be changed, and the distribution within medicine needs changing. Economic factors are important in justice, but so are attempts to justly meet the different needs of people, some of whom will need more. Often genetics counseling is seen in light of a cost-benefit ratio, but that type of analysis is too simplistic. Financial considerations should not alter clinical behaviour, such as the encouragement of selective abortion because of the costs to society, even though patients as individuals may take that and especially their families' own costs, into account.

Between different people's there are many similarities. There are also universal human rights which should be protected, and international medicine should recognise these. More discussion of specific areas of applied genetics is presented after the next section. This book attempts to consider the broader issues of life, and beyond our interation with each other to our interaction with the environment. There are some implications of the use of genetic technology, and also some lessons, that we must discuss.

Sustainable Living

In the final decade of the twentieth century we should be becoming increasingly aware of the need for moving to a system of sustainable living. In order to accomplish this, we not only have to view the environment in its role as essential to human existence, but we should value the environment for what it is. We need to promote the awareness of the values of the environment and other creatures.

To those of us that live in developed countries that can be accomplished by directing people's focus to the beauty of nature or the diversity of animal and plant life. However, to the starving in the desert this concern is unimportant. If we put ourselves in their place we would also put the environment in a secondary place of importance, the primary concern being survival of oneself and family. If we want to provide food and housing to those people, we may need to use more of the forests or natural habitats for agricultural land. The causes seem to clash. The challenge is

to attempt to alleviate the root problems.

Biotechnology will change the way we live. Already we see examples where it has changed the situation of some groups. For example, dwarfism caused by the absence of growth hormone should no longer afflict our children, as the hormone can be made cheaply, in unlimited quantities. Of course, in this example we see the case of a condition that while not being a major handicap, became one because of the social stigmatisation of people suffering from the condition. If we changed the way we think, it would be a better solution. Many more common products will become available. It may be the new range of washing powders, or the new ways of growing crops that have more daily impact. Medical care is also aided.

At a practical level this involves several major changes. Birth control is essential, to reduce the numbers of humans, this is a medical and political issue. Fairness in the distribution of food and materials would decrease the needs of the poor, an economic and political issue. More efficient agriculture will also reduce the the land that is required for agriculture, a scientific issue. Reducing consumption will aid this, an issue that the public as individuals must change.

The genetic technology described in this book considers the improvement of agricultural efficiency. There has to be further discussion of the commercial aspects of biotechnology. We need to implement these changes to succeed. Changing the way human beings behave towards each other is a supernatural task, that can be aided by all of us changing our attitudes. We must ensure that efficient and sustainable agriculture is encouraged, but recognise it is only part of a broader solution. Sustainable living involves not just efficient agriculture, but also minimising our energy use and pollution. It involves changing public policy. It involves changing the way people think. For the scope of this book the issue is our use of agriculture and including agricultural industry. We must realise how important the use of new technology is when it aids this process, and work towards this goal.

Sustainable Agriculture

Sustainable agriculture could be defined as the appropriate use of crop and livestock systems and agricultural inputs supporting those activities which maintain economic and social viability while preserving the high productivity and quality of the land (Hassebrook & Hegyes 1989). Current research interests in biotechnology may not be the best way to provide sustainable agriculture. Large corporations are developing new techniques that may require constant, or at least annual, application. In the USA about 0.5 billion tonnes of toxic active ingredients are applied to farmland annually, with only 1% reaching their target. There has been little research into more longterm controls, and cynics can claim that this is because the companies will make more money out of repeated application products. The use of Bacillus thuringiensis against corn borers is one such trade-off; corn borers tend to persist in fields where corn is planted year after year in a monocrop system. It may in fact be better to use crop rotation for control of pests.

One controversial research application is the development of herbicide-tolerant plants. Herbicide tolerant plants may actually increase the amount of chemicals used, though this is denied by the companies producing them (Anderson 1989). One of Monsanto's projects is to develop soyabean varieties resistant to their herbicide Roundup. These varieties would increase the sale of Roundup, already

the world's largest selling herbicide, by at least US$ 150 million. The insertion of Basta resistance into potato, tobacco and tomato plants is expected to earn Hoechst another US$ 200 million a year. The world's largest corn seed producer, Pioneer HiBred is using a gene given to them by American Cyanamid for resistance to the imidizolinone family of herbicides. In return the company will sell herbicide. Soybeans resistant to Ciba-Geigy's atrazine herbicides, could increase annual herbicide sales by US$ 120 million(Fowler et al. 1988). Restructuring of the seed and agrochemical firms is occurring. For example Calgene has patented the GlyphoTol herbicide tolerance gene for cotton, and in 1987 it acquired a cotton seed company, to establish control over the breeding of resistant cotton (Juma 1989).

To determine what effect herbicide tolerant plants will really have on herbicide use further study needs to be done. A recent American Report (BWG 1990) was very critical of the use of public funds to develop herbicide tolerant crops, and this may be stopped in the USA. They argue that research should be aimed at growing crops without herbicides and chemicals, even if they are biodegradable. An alternative would be to increase the tolerance of crops to mechanical cultivation which can also be used in weed control. Many chemical companies have obtained seed company interests, and will market the products together. The answer is not known.

The certainty is that there is a lack of research into biological controls, most developed countries use high input agriculture, and conduct little research into biological control. Biological weed control may be the only practical solution in some situations, such as the control of alien weeds in tropical forests. Overall, about one case in six has worked, but it is very cost effective (most projects cost less than US$ 150,000) (Crawley 1989). This success rate is still much greater than that achieved in searching for useful agrochemicals. It may be best to use government funding for more biocontrol, and leave funding for herbicide tolerant crops to those companies that will profit from such varieties through sales of herbicide.

While there are valid criticisms about the development of herbicide-tolerant plants, they do have immediate environmental advantages. For example, maize growers make 4-6 herbicide applications a season, but if the crop was tolerant to a broad-spectrum post-emergence herbicide only one application would be needed. Not only the amount of herbicide would be less, but as mentioned, a biodegradable herbicide could be used. It is important that biodegradable herbicides are used, for example atrazine is not biodegradable, and Ciba-Geigy has recently dropped their soyabean project because of this. It would also been difficult to obtain Environmental Protection Agency (EPA) approval for large scale use. Roundup may also be persistent in surface water and is toxic to fish (BWG 1990). Reducing herbicide use and switching to biodegradable products is consistent with sustainable agriculture and is an important practical step in that direction. The safest herbicides may be those that interfere with the biosynthesis of essential amino acids in plants, such as glyphosate, sulfonylurea and imidazolinones (Schulz et al. 1990).

Criticism has also been made at the use of bovine somatotropin (BST). Although it increases milk production, it may have negative effects on farmers. It may leave the dairy industry in the hands of industrial type farmers. There are those that say that even if small farmers lose their farms, we should always work for greater efficiency. However, this has major social repercussions that should not be left in the hands of people of only one interest group. Industrialised countries do

protect small farmers to avoid the social costs, as seen with the rice farmers in Japan. This was discussed in chapter 10. There are major consequences of the new technology and it may not always be right to pursue it.

One hundred years from now the earth will probably have ten billion humans, about twice its current population. There should be enough food production, but that is not the major question. Yields have been increasing linearly for the past three decades in major crops such as wheat, maize and sorghum. At least half of the gains are because of genetic improvements (Duvick 1984). Food production must expand in a way that does not destroy the natural environment. For this to happen, new technologies that minimise erosion, desertification, salinisation of the soil, and other environmental damage, must be introduced. The most difficult problem is not just developing technology, but getting farmers to use environmentally sustainable technology (Crosson & Rosenberg 1989). Alternatives to current practises need to be developed, including crop rotation, integrated pest management, health maintenance as well as using GMOs (CRAF 1989). All alternatives need to be tested. Current economics do not consider the environment and its value, and this needs to change. By taking into account the value of the environment, we are thinking of long term interests, something that is not considered in most modern economic policies. A target of genetic engineering is to increase the quality of foodstuffs, rather than the quantity. This is an important goal for world agricultural research to concentrate on.

Controlled Progress

From a consideration of the developments in molecular biology and genetics, and their likely applications in the near future, it is possible to decide which areas promise benefits and in which areas there are ethical dilemmas, and where we need to stop.

There have been a wide variety of concerns expressed over genetic engineering. These are genuinely important. They fall into two basic classes: those which depend on personal opinions, and those which depend on science (such as risk assessment). The concerns of the first type were the basis of chapters 3 and 6. They are important for the future development of genetic engineering and the limits to its application. With the wide range of implications to society, society needs to decide. However, in order to do this, public education is required.

Regulation of Genetic Engineering

The use of recombinant DNA techniques has aided the progress of biology and is now central to biological science. It should continue, within the containment facilities seen to be necessary by the established safety committees. The insertion of new genes into plants and microorganisms should be unlimited in the laboratory situation. Except all biological warfare research should be stopped.

Regulations need to consider international work, as considerable research has been conducted into developing safe regulations. The special concerns of each country need to be respected. Some questions, such as the safety of GMOs for industrial use or free release, and food safety, are scientific questions. The

decisions whether to use a new organism are more open to the public, and will be determined in the end by consumer choices. Other questions, such as animal patenting, and the level of animal use that is permitted will be more subject to public opinion.

Agricultural Uses of Genetic Engineering

In agriculture there are definite advantages for some artificial reproduction, embryo transfer, clonal reproduction, and genetic engineering. This does not raise great ethical dilemmas if there is no harm done to the animals (further than their growth for human consumption).

The main concern about transgenic plants and microorganisms is the question of environmental release, and safety of the foodstuffs. The key principle involved is one of stewardship of the earth. We can see some of the many advantages that this new technology does have, but we do need to be careful in case it does result in the wide distribution of certain detrimental genes in the ecosystem. These advantages include increased production with reduced costs. The reduced costs include economic costs, such as reduced quantities and simpler use of herbicides and pesticides; and environmental benefits from the reduced use of agrochemicals and the substitution of older toxic products with biodegradable products.

Need to Consider Broader Implications

Some concerns, such as commercialisation and sustainable agriculture are broader issues. They are more questions about how we should apply these techniques, who should use them, whether they should expect great profits from them, and other political concerns. While these concerns are important, they are not significantly affected by the actual use of the new techniques. However, we may need to focus more attention on the implementation of biotechnology itself, rather than the safety of individual GMOs. It has greater implications, extending to social changes, than do the low risks of ecological harm associated with small scale GMO release.

The decisions in the area of biotechnology must take into account many considerations, extending well beyond the scientific merit of a particular technique, or the opportunities suggested for its application. These decisions are often difficult or controversial which makes good public relations important. Independent regulatory control is well established in many countries. The procedures used in risk evaluation, and procedure, may need revisions.

Animal Experimentation

The problems of transgenic animals come down to two major issues, environmental release and ecological dangers, and issues covered under the idea of vivisection, such as making animals that are diseased or for the sake of a better word, very unnatural. There is the need to develop the regulations further with criteria for judgement less based on pain as argued above. There is room for government legislation to supplement the regulations based on avoidance of pain and endangered species.

The insertion of new genes into animals should continue where necessary for the study of biology when there is no clear detrimental affect upon the mutant animals. There is a balance in situations between importance of an experiment and

the effect and the status of the animal. We must examine where the boundaries could be drawn (Macer 1990a). In the case of higher animals such as primates or dolphins there is sufficient doubt regarding their status not to use them for animal experiments. In the case of trials of gene therapy if this type of animal does not possess the disease then it would seem unethical to inflict the disease and attempt gene therapy. The human trial will in the end be experimental, even after several primate trials. However, if an other animal such as mice or sheep can be used, it would be ethical to use a controlled number, provided that the animal is in plentiful supply. In certain cases such types of animals may be made diseased and bred as a strain, there are limits depending on the suffering and the example. The general question of under what conditions experimental use of animals is justified, should follow the existing law, i.e. only when a scientifically important result can be obtained with little animal suffering, and there are no alternative experimental subjects.

Regulate Use of Infertility Treatments

Techniques for the alleviation of infertility in married human couples should continue to be developed, and improved, especially IVF. However, the use of extramarital gametes should be under tighter control,with the recommendation of suitability being made by several independent physicians. The donors of the gametes should be anonymous, but with longterm medical records held by the central government. The children should be told of their origins, but I'm unsure whether they should gain access to the records of their genetic parents when they are 18 years old.

No gametes, or embryos should be commercially sold. Commercial surrogacy is ethically unacceptable, despite its acceptance in some countries. In exceptional cases the offer of surrogacy from a friend or relation may be appropriate. The judgement of when surrogacy could be used in a noncommercial arrangement may need to be considered by the central licensing authority, after recommendation from several independent physicians.

Regulated Research on the Early Human Embryo

In some limited areas of clinical importance, when all possible, useful preliminary experimental results are known, it may be right to conduct experiments of human embryos up to the age of 14 days if there is no alternative. The use and licensing of such experiments, including the approved numbers of embryos and their source, should be in the control of a central licensing authority in each country. The status of the human embryo up to 14 days in my opinion is less than some higher animals that have a strong sense of self-awareness and some rationality.

Encourage Use and Development of Birth Control

The use of contraceptive, birth control methods, even if they involve the death of embryos up to 14 days old, are acceptable. Contraception in general, is not only ethical, but the alternative consequence of not using them may mean overpopulation which is undesirable for the proper stewardship of the world's population. It is wrong to impose compulsory birth control policies on the general population, but it should be strongly encouraged and possibly by financial incentives.

As with other medical services, within the priorities established for each country there should be equal and fair access to all genetic services for every person.

Use of Genetic Screening Early in Fetal Development

Abortion in general is ethically difficult, except if before the embryo is 14 days old. Selective abortion may need to be considered for some exceptional diseases, and should be done at an early an age as possible, up to a general age of 6-8 weeks. Beyond the beginning of brain life it is unethical, but is still not murder until the age of viability. There should be research into ways of screening at earlier times, and use of chorionic villi sampling where possible. As well as genetic screening, there should be education of other risk factors in pregnancy, such as alcohol or smoking, which may be the cause of some mutations, and birth handicaps. All approaches are required. For couples who have a high risk of transmitting a serious genetic disease, it may be ethically preferable to use IVF with a donated gamete.

Access to IVF treatments or embryo flushing/screening and embryo transfer clinics will increase, but it is probably only applicable to known carriers of genetic disease that do not agree with selective abortion. The general population screening requires a method for in vivo screening, which can occur only after about 6 weeks after conception with the best of current chorionic villi sampling. It is hoped that maternal blood screening will be developed. There are five important criteria for genetic screening followed by selective abortion; the test must be accurate, the disease serious, the costs reasonable,there should not be effective therapy available, and the patient, with family, should decide.

Careful Regulation of Genetic Information

Our genetic knowledge is increasing at a tremendous rate, which is good. New genetic knowledge will result in cheaper, faster and more accurate genetic tests. However, society is not yet equiped to receive this information. After receiving it, it must be ethically used. There need to be decisions on what information to tell, to whom it should be told, when in life, and how. There will need to be coordinated programs after research is done on the implications of this knowledge at different stages of life, in peoples life decisions.

The establishment of government genetic registrars may be beneficial to overall health provision and genetic research. However, these registers have many problems arising from possible abuse. Even if a computer system is protected, we can envisage possibilities for illegal searches of such data. There are also many problems of family confidentiality. Until sufficient protection measures are in place, it is not good to begin widescale genetic registers.

It is important to protect individuals confidential data from several groups in particular; the employers and from medical insurance companies. Even if there is no systematic genetic screening of applicants for medical insurance at present, it is effectively carried out by asking questions about family genetic disease. This information should also be protected in a just health care system. In the case of employers, rather than screening workers they should clean up the work environment, as most risk factors work in terms of degrees. While some people are genetically very sensitive to some chemicals, other people will generally be somewhat sensitive to such chemicals any way, such as asbestos. The primary

assessment should be in terms of job proficiency, which for certain jobs could be checked very frequently.

Ban on Nondisease Genetic Selection

Many "minor" diseases which are currently considered as grounds for selective abortion, do not seem to be sufficient to justify the use of abortion. In this category I would include those diseases which are currently treatable and curable by medicine (e.g. some types of haemophilia), and other diseases such as albinism which are just regarded undesirable. Sex selection or other nondisease selection is unethical. It is better for society to change than to mould birth control to please the current desires of some members of society, that may be based on prejudicial views.

Somatic Cell Gene Therapy Should be Encouraged

The use of somatic cell gene therapy should be promoted as a new medical technique which will complement bone marrow transplantation and other symptomatic disease treatments. Before it is widely conducted on humans it should have extensive trials, first on animals and then on humans. The first use of the therapy will depend on the estimated safety, efficiency and need of each individual patient. Initially it may require central control from a licensing authority, but once established it should be under the same control as for the use of other medical techniques. Excessive levels of committee approval is inefficient and unnecessary.

Temporary Ban on Germline Gene Therapy

Germ-line gene therapy should be banned until safety is assured, but the ban should be reviewed. The judgement on which diseases are to be treated can be made by the use of common sense, public discussion and a central licensing authority. Safety needs to be tighter than for the use of somatic cell gene therapy. Governments should never enforce germ-line gene therapy on consenting individuals, but therapy may be enforced on the fetus if necessary for survival.

Encourage Alternatives to Germline Manipulation

To examine the alternatives, it is important to look at the goal of the technique. From the parents perspective, it is aimed at producing a healthy child. At an individual level it is aimed at leading to a healthy life, including reproduction. At a societal level, it is aimed at reducing the number of people in the next generation who suffer from genetic disease. There are benefits to all. Society's goal must be accomplished without infringing individual rights.

With the advent of embryo screening, there must be serious doubts as to when positive germ-line manipulation is appropriate. It would not seem appropriate in the case of recessive genetic diseases, as it will be possible to select those embryos that do not have the disease-causing genes, implanting only those which are normal. Human beings share with the rest of living organisms the capacity to produce large numbers of offspring, so there will be sufficient embryos produced to satisfy most people's urge to have their own germ-cells involved in their offspring. At this stage of development the options are abortion or somatic therapy, it is past the time of what we could consider germline embryo manipulation. The alternatives should practically limit the application of germline manipulation, until some currently unthoughtof technological development.

While we may try to save the life of handicapped fetuses from 6 months after conception, is it worth saving the life of an 8-cell embryo, when others are present. Part of the answer to this rests with our ideas of a human embryo. This is a very contentious issue, especially when brought out of context. The ethical support for this alternative is supported by the concept of individual origins being after the formation of the primitive streak (Ford 1989), about 15 days after conception. However, there are important concerns about the considerable amount of resources necessary to make gene therapy a reality, and the limited number of conditions and persons to which it could apply.

The overriding factor at present is the experimental risks to the growing child, after germline therapy. Parents do make decisions regarding the future of their children already, as does society. There is some prerogative for future germline therapy. However, if there is no proven therapy, early selective abortion is an option that many parents consider preferable.

Laws Needed to Prohibit Genetic Discrimination

There needs to be some laws made to prevent genetic discrimination. This may mean making genetic information private, or else having an effective and fair public health service. To allow genetic discrimination is clearly unethical, and one of the major social implications of the new genetic technologies. It may be desirable to screen every fetus or individual, but only if they can be protected from discrimination, and only when it is accompanied by sufficient counseling and education. We all carry genetic disorders and it is important that we work to help those people who have them. The United Nations could support a call for genetic equality.

Not only is discrimination a problem, but so is stigma. People can misinterpret information in idiosyncratic ways. Parents may feel guilty of transmitting a abnormal allele of a gene to children, even if they are only carriers. We must stress the universality of recessive disease alleles, we all have them. People may be afraid to tell others once they learn they have an abnormal gene. In some countries the young adults may be encouraged to hide the information so that they do not become nonmarriable. They may be later guilt reactions, and other psychological problems.

Education of Genetics

The new techniques will be of no use unless people are educated about them. There are different levels that need to be targetted, and all information should be appropriate for those people, including cultural and religious factors. The health care workers need some basic training in genetics, and genetic counseling. Specialist genetic counselors are also required, as are laboratory personnel to develop and run the tests. Voluntary counselors may also be necessary, as the number of people trained is much less than the need. The public must know some basics before they can be informed consumers and users of these services. This means that this information must be given at early school stage, and beyond. The language of probability and risk is important, how to perceive a 25% risk of a child with a serious disease.

Unless the public is educated, and informed about a genetic screening programs, even if it is voluntary and non-directive, in effect it can be the same as if

the program was mandatory if the government was authoritarian. It is therefore essential for the public to be educated to ensure they can chose.

New Possibilities should be Pursued

The approaches used here provide a basis for approaching other issues in bioethics, as the progress in biology and medicine continually opens new doors which society must decide whether to enter. Morality concerns itself with the rightness or wrongness of human conduct. Law, or public policy, is concerned also with the public good. The important criteria of feasibility is important, involving questions such as whether the policy will be obeyed, whether it is enforceable, are there other bad effects on society? We need to examine what conclusions are appropriate to put into law. If attempting a compromise between incompatible moral positions and of proposing arbitrary legal limits, there will be many critics, as was seen of the Warnock Committee report, and most other similar proposals. The law can not be an expression of everybodies moral feeling, the law applies to everyone and must be enforceable. Rather than what is ethical, we have to ask where a law should intervene to control a process, and when it should make something criminal. We can not always follow some imagined "common morality", as no set of principles is yet to be agreed on, but we must try.

All of society has to decide the moral problem, not only the scientists. Scientists must be held responsible for their actions. We need to examine what type of society we are making for ourselves. Science is the most powerful agent of change in our world, and genetics promises much more than a revolution in our medical treatments. We should learn how to handle it so that it is not misused, and learn how to anticipate the new directions the use of gene therapy may take. It must be clear to all of us that science will not solve our social problems, but it is an important part of our management of the earth.

Changing Our Perspectives

When we think of life on this planet we have different images. Our picture of life is changing, shaped by the world. Within different religions we have seen that there are different perspectives, and at the grassroots level, we may not yet even be aware of what the real feelings of people are. Our views of life are challenged and to some degree moulded by new technology, new circumstances in which we find ourselves. There may be some good in this, if our view violated someone else's autonomy, such as sexism or racism. It may also be good if it makes us more respectful and appreciative of the world in which we live.

A fundamental part of the process is to discover what images of life are. This should be pursued in different cultures and is a prerequisite to understanding the impacts of new technology (Morioka 1988). Life may mean many things, and it constitutes many things, interacting together.

We should develop a view that is applicable to all of life. The development of this view will require participation by people from all walks of life, and from all types of research speciality. The term bioethics should mean the study of life ethics, but it has often been viewed only as a part. The concern with medical ethics has meant that while many people, or committees, are called "bioethics" committees, they only consider medical ethics. There is also a point for those who consider

environmental ethics apart from human-human interactions, again it is an incomplete perspective. I hope that this book, which attempts to combine both topics in the same cover, may help those in one field grasp more of the issues in the other. We have much to learn from our approaches to genetic technology, not just the nature of our genes, but the nature of our thinking about what is important in life.

Genetic Engineering is a Catalyst for Bioethics

Genetic engineering makes us challenge our technology, and think about limits to advance. We are probed into searching for answers to questions. At the end of this book, more questions follow what may have been some answers. We need to consider many questions, some are:

* Why do we think genes are so fundamental, and should we?

* Why do we value nature, and what occurs naturally? Disease is a natural event, but we try to cure or treat it. We must grow food at least, even if we don't eat meat. We accept the idea of living in a city, where are the limits?

* Why should we object to mixing the genes from different species?

* What is our reason for placing limits on animal abuse, and does pain make the difference, or some other type of property, such as life itself?

* Are we happy about eating genetically modified food, when we already eat food made from genetically breeding of crops and animals? Do we want to avoid using pesticides, which pollute our environment? The vegetables and crops that are made, also the meat and fish, are much healthier for us than the softdrinks and crisps and beer that we consume. Will it make us more conscious of our diet?

* What is the cost versus benefit ratio we are prepared to accept? What risks will we accept, for example of a GMO upsetting the ecological balance of an area? Will we accept the risks of continued pesticide use? There are many other issues.

* Do we object to commercialisation of genetic material, and animal patents?

* It makes us think about what a human person is;
    Should we do genetic screening and selective abortion?
    At what stage during fetal development does an embryo become a person?
    What diseases justify this selection?
    Should we allow eugenics?
    Should we allow germline genetic therapy, or manipulation?
    What do we value in our lives and in others?

* Should people have reproductive freedom? What are the limits? Should we ban sex selection? Should we allow positive genetic selection of gametes, or genes; we allow people to use cosmetic surgery?

* Should governments control reproduction?

* How much technology should we use? Enough to fix the mistakes of the past, enough to sustain a large human population living in a sustainable way on the planet? When will our pursuit of technology be reduced?

* What will happen in fifteen years when we know the entire human genome sequence? The problems of genetic discrimination by employers or medical insurance are so great that it may force national health systems. A good result, but it may also lead to genetic determinism. People may think they can only do what their genes allow them. There must be limits to the use of this knowledge. It is justified by all the medical benefits, but it has many challenges.

* What will humanity become. Do we want to preserve parts of our society's values?

* What are our responsibilities to future generations, can we become responsible?

Basically, genetic engineering makes us think about life.

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Glossary

Abortion: The spontaneous or deliberate termination of pregnancy before the embryo or fetus has been born, or is viable outside the womb.
AID: Artificial insemination using donor sperm (see *artificial insemination*)
AIDS: Acquired immunodeficiency syndrome
Alleles: Alternative forms of a genetic locus; alleles are inherited separately from each parent (e.g. at a locus for eye color there might be alleles resulting in blue or brown eyes).
Amino acid: Any of a group of 20 molecules that combine to form proteins in living things. Chemically they contain an amino group, $-NH_2$, and a carboxyl group, -COOH. The sequence of amino acids in a protein is determined by the genetic code.
Amniocentesis: Diagnostic sampling of the amniotic fluid during pregnancy, usually performed by insertion of aneedle into the amniotic fluid which surrounds the fetus during pregnancy. Performed for prenatal screening.
Anencephalic: Literally the condition of having no encephalon or brain (normally applied to fetuses or infants with no cerebrum).
Anesthesia: The partial or complete loss of sensation with or without consciousness as the result of injury, disease, or administration of an anesthetic.
Animal: A living being with a capacity for spontaneous movement and a rapid motor response to stimulation. Animals can be divided into two groups, invertebrates (animals without backbones) and vertebrates (animals with backbones).
Antibiotic: Substance derived from a fungus or bacterium that inhibits the growth of other microorganisms.
Antibody: A blood protein (immunoglobin) produced by white blood cells in response to the presence of a specific foreign substance (antigen) in the body, with which it fights or otherwise interacts. Antibodies to sperm, if present, can impair fertility by causing agglutination of sperm.
Antisense RNA: RNA that is complementary to the nucleotide sequence of normal mRNA. It therefore forms a duplex with the mRNA preventing the mRNA being used in protein synthesis, thus indirectly controlling gene expression.
Artificial insemination: The introduction of sperm into a woman's vagina or uterus by noncoital methods, for the purpose of conception (see *AID*).
Asexual reproduction: Reproduction of organisms by purely vegetative means without the function and interaction of the two sexes. Examples of asexually reproduced plants are roses, peach trees, and lilies.
Autonomy: The governing of one's self according to one's own system of morals and beliefs.
Autoradiography: A technique that uses X-ray film to visualize radioactively labeled molecules or fragments of molecules. For example it is used in analyzing the length and number of DNA fragments separated by electrophoresis.
Autosome: A chromosome not involved in sex determination. The diploid human genome consists of 46 chromosomes, 22 pairs of autosomes and 1 pair of sex chromosomes.
Bacteria: Single-celled, procaryotic organisms that reproduce by binary fission.

Bacteriophage: A virus which infects bacteria.
Baculovirus: A virus whose host is a bacterial cell; also called phage.
Base pair: Two nucleotides (adenosine and thymidine, or guanosine and cytidine) held together by the bonds between individual bases.
Beneficence: The state of doing or producing good; compare to nonmaleficence.
Biopsy: The sugical removal of a cell or sample of tissue for diagnostic purposes.
Biotechnology: The use or development of techniques using organisms (or parts of organisms) to provide or improve goods or services.
Birth control: The prevention of birth.
Blastocyst: A hollow ball of cells, filled with fluid, that forms about four days after fertilization from the zygote, and prior to the beginning of the process of implantation. The embryo develops from a small cluster of cells in the centre of the sphere, and the outer wall of the sphere becomes the placenta.
Blastomeres: The daughter cells that derive from the first and subsequent cleavages of the zygote.
Caesarian: The surgical removal of a fetus through an incision in the pregnant woman's abdominal tissue and uterine wall.
Carcinogen: Substance that causes or increases the risks of getting cancer.
Carrier: Someone who may transmit a genetic condition but who normally does not show any evidence of the disease.
Cell: The smallest component of life. A membrane-bound protoplasmic body capable of carrying on all essential life processes. A single cell unit is a complex collection of molecules with many different activities all integrated to form a functioning, self-assembling, self-regulating, and self-reproducing biological unit.
Cell culture: The propagation of cells removed from multicellular organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements.
Cell fusion: The joining of the membrane of two cells, thus creating a single hybrid cell that contains nuclear matter from both the parent cells.
Centimorgan: A unit of measure of genetic recombination frequency. One centimorgan is equal to a 1 percent chance that a genetic locus will be separated from a marker due to recombination in a single generation. In human beings, 1 centimorgan is equivalent, on average, to 1 million base pairs.
Centromere: The small junction area between the two arms of a chromosome.
Chimera: An organism formed by the aggregation of cells taken from different genotypes. Chimeric embryos may occur naturally or artificially. An inter-species chimera is when the cells are from different species.
Chloroplast: Those structures within plant cells where photosynthesis occurs. They contain small circular DNA molecules that replicate independently of the nucleus.
Chorionic villi: Finger-like projections growing from the external surface of the chorion that contribute to the formation of the placenta.
Chorionic villi Sampling (CVS): The procedure used in prenatal diagnosis to take a small sample of the chorionic villi for testing, such as genetic screening.
Chromosomal abnormalities: Genetic mutations involving changes in the number and structure of chromosomes.
Chromosome: A structure that lies inside a cell's nucleus. A chromosome is composed mainly of DNA. Each normal cell of the human body has 23 pairs of

chromosomes.

Cleavage: The stage of cell division that takes place immediately after fertilization and that lasts until the cells begin to segregate and differentiate and to develop into a blastocyst.

Clones: A collection of cells or organisms that are genetically identical.

Cloning: The process of asexually producing a group of cells (clones), all genetically identical to the original ancestor. In recombinant DNA manipulation procedures to produce multiple copies of a single gene or segment of DNA.

Codon: A sequence of three DNA base pairs which codes for an amino acid.

Complementary DNA (cDNA): DNA that is synthesized from a messenger RNA template; the single-strand form is often used as a probe in physical mapping.

Conception: The fertilisation of the egg by a sperm that initiates the formation of a zygote (has been used for implantation also).

Conceptus: This term refers to the products of fertilization. It includes the embryo proper as well as extraembryonic structures and tissues that develop from the zygote (e.g. placenta). It is also called the *preembryo.*

Confidentiality: A fundamental component of the physician-patient relationship, stemming primarily from the Hippocratic oath, in which the physician has the duty to keep confidential all that is confided by the patient.

Conjugation: The reproductive process by which DNA is transferred between bacteria during cell-to-cell contact.

Consanguinity: Descent from common ancestors.

Consequentialism: The normative theory that the rightness or wrongness of actions is determined by anticipated or known consequences, compare to deontologism.

Contigs: Groups of clones representing overlapping, or contiguous, regions of a genome.

Copyright: Copyright protection applies to eight categories of works: literary; musical; dramatic; pantomime and choreographic; pictorial, graphic and sculptural; motion pictures and audio-visual work; sound recording; and computer programs. Copyright protects the expression of an idea, not the idea itself.

Covenant: A solemn agreement between two or more parties.

Crossing over: The breaking during meiosis of one maternal and one paternal chromosome, the exchanging of corresponding sections of DNA, and the rejoining of the chromosomes.

Cryopreservation: The preservation of sperm, embryos and oocytes by freezing them at extremely low temperatures.

Cultivar: An international term denoting certain cultivated plants that are clearly distinguishable from others by one or more characteristics and which when reproduced retain those characteristics. In the USA "variety" is considered to be synonymous with cultivar (derived from cultivated variety).

C-value paradox: The lack of correlation between the amount of DNA in a haploid genome and the biological complexity of the organism. (C-value refers to haploid genome size.)

Cystic fibrosis: Disease which affects the sweat and mucus-secreting glands, resulting in chronic lung disease, pancreatic insufficiency, abnormally salty sweat, and in some cases, liver disease.

Cytoplasm(ic): The substance within a cell external to the nuclear membrane;

pertaining to or contained in the cytoplasm.
Deletion: Loss of part of a chromosome.
Deontologism: A theory according to which actions are judged right or wrong based upon inheredt right-making characteristics or principles rather than on their consequences.
Determinism: The theory that for every action taken there are causal mechanisms such that no other action was possible.
Diploid: A full set of genetic material (two paired sets of chromosomes), one from each parental set. All cells except sperm and egg cells have a diploid set of chromosomes. The diploid human genome has 46 chromosomes (see *haploid.*).
DNA, deoxyribonucleic acid: The molecule that encodes genetic information. DNA is a double-stranded molecule held together by weak bonds between base pairs of nucleotides. There are four nucleotides in DNA: adenosine (A), guanosine (G), cytidine (C) and thymidine (T). In nature, base pairs form only between A and T and between G and C, thus the sequence of each single strand can be deduced from that of its partner.
DNA probes: Segments of single-strand DNA that are labeled with a radioactive or other chemical marker and used to identify complementary sequences of DNA by hybridizing with them (see *hybridization.*).
DNA sequence: The relative order of base pairs, whether in a stretch of DNA, a gene, a chromosome, or an entire genome.
Domain: A discrete portion of a protein with its own function. The combination of domains in a single protein determines its unique overall function.
Dominant: A trait or condition which is expressed in individuals who have a single version of a particular gene.
Donor gametes: Eggs or sperm donated by individuals for medically assisted conception.
Double effect, the Doctrine of: The theory that an evil effect is morally acceptable provided a proportional good effect will accrue, evil is not intended, the evil effect is not the means to the good, and the action is not intrinsically evil.
Double helix: The shape in which two linear strands of DNA are bonded together.
Ectopic pregnancy: A pregnancy that occurs outside the uterus, usually in a fallopian tube.
Egalitarian: A social philosophy that advocates human equality.
Electrophoresis: A method of separating large molecules (such as DNA fragments or proteins) from a mixture of similar molecules. An electric current is passed through a medium containing the mixture, and each kind of molecule travels through the medium at a different rate, depending on its electrical charge and size. Separation is based on these differences.
Embryo: Early or preimplantation embryo refers to the first two weeks after the formation of the zygote. Embryo technically refers to the stage from the third to eighth week fo development. Often the term embryo also encompasses development from the beginning up to the eighth week.
Embryo donation: The transfer from one woman to another of an embryo obrained by artificial insemination and lavage or, more commonly, by IVF.
Embryo lavage: A flushing of the uterus to recover a preimplantation embryo.
Embryo transfer: The transfer of an *in vitro* fertilized egg from its laboratory dish into the uterus of a woman.

Endogenous: Developing or originating within the organism, or arising from causes within the organism.

Endotoxin: Poison produced by some gram-negative bacteria, present in the cellular membrane, and released only upon cell rupture; composed of complex lipopolysaccharide (fat-like molecule and sugar molecule) and more heat-stable than protein exotoxins.

Enzyme: A protein that acts as a catalyst, speeding the rate at which a biochemical reaction proceeds byt not altering its direction or nature.

EPA: Environmental Protecion Agency of the USA.

Episome: A DNA molecule that may exist either as an integrated part of a chromosomal DNA molecule of the host or as an independently replicating DNA molecule (plasmid) free of the host chromosome.

Ethics: A system of moral principles or standards governing conduct.

Eucaryote: Cell or organism with membrane-bound, structurally discrete nucleus and other well-developed subcellular compartments. Eucaryotes include all organisms except viruses, bacteria and blue-green algae. Compare *procaryote*..

Eugenics: Attempts to improve hereditary qualities through selective breeding. See *positive eugenics, negative eugenics, eugenics of normalcy.*

Eugenics of normalcy: Policies and programs intended to ensure that each individual has at least a minimum number of normal genes.

Euthanasia: The merciful hastening of death, often limited to willful and merciful actions to kill of one who is injured or terminally ill.

Exons: The protein-coding DNA sequences of a gene. Compare *introns.*

Exotic: Describing a species not originating in the place where it is found; a nonnative, introduced species.

Exotoxin: A poison excreted by some gram-negative or gram-positive organisms. It is composed of protein.

Extrachromosomal DNA: DNA not associated with the chromosome(s), for example, plasmid DNA or organelle (mitochondria or chloroplast) DNA).

Fallopian tube: Either of a pair of tubes that conduct the egg from the ovary to the uterus. Fertilization normally occurs within this structure. Blocked or scarred fallopian tubes are a leading source of infertility in women.

Fermentation: The process of growing microorganisms.

Fertility drugs: Compounds used to treat ovulatory dysfunction. Thise include clomiphene citrate, human gonadotropins, bromocriptine, glucocorticoids and progesterone.

Fetus: The developing human individual from the ninth week after fertilization until birth.

FDA: Food and Drug Administration of the USA.

Fertilisation: The event that initiates the development of an oocyte into embryonic developemnt, normally triggered by the entry of a sperm into the oocyte.

Fingerprinting: The technique of DNA fingerprinting is used to uniquely characterise individual organisms, foods, or biological samples, based on their DNA composition (can also fingerprint chemicals and proteins).

Follicle: The structure on the ovary surface that nurtures a ripening oocyte. At ovulation the follicle produces estrogen until the oocyte is released, after which it becomes a yellowish protrusion on the ovary called the corpus luteum.

Food: Anything consumed or sold for animal consumption.

Food additive: A minor ingrdient added to food to achieve a specific effect. In law, some of these compounds are legally excluded from being calledthis term for the purposes of food safety regulation.

Frameshift: Mutation that results when the genetic code is read beginning at the second or third base of a codon.

Gamete intrafallopian transfer (GIFT): A technique of medically assisted conception in which mature oocytes are surgically removed from a woman's body and then reintroduced, together with sperm, through a catheter threaded into the fallopian tubes, where it is hoped fertilization will take place.

Gamete: Mature male or female reproductive cell with a haploid set of chromosomes (in humans there are 23 chromosomes); that is, a sperm or ovum.

Gene: The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome. See *gene expression.*

Gene expression: The process by which a gene's blueprint is converted into the structures present and operating in the cell. Expressed genes include those that are transcribed into mRNA and then translated into protein and those that are transcribed into RNA but not translated into protein(e.g., transfer and ribosomal RNAs).

Gene families: Groups of closely related genes that make similar products.

Gene product: The biochemical material, either RNA or protein, made by a gene. The amount of gene product is used to measure how active a gene is; abnormal amounts can be correlated with disease-causing genes.

Genetic code: The sequence of nucleotides, coded in triplets along the mRNA, that determines the sequence of amino acids in protein synthesis. The DNA sequence of a gene can be used to predict the mRNA sequence, and the genetic code can in turn be used to predict the amino acid sequence.

Genetic linkage map: A map of the relative positions of genetic loci on a chromosome, determined on the basis of how often the loci are inherited together. Distance is measured in centimorgans.

Genetic screening: Analysis of an individual genotype for the presence or absence of a particular DNA sequence, or gene.

Genetics: The study of the patterns of inheritance of specific traits.

Genome: All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genome projects: Research and technology development efforts aimed at mapping and sequencing some or all of the genome of human beings and other organisms.

Genomic library: A collection of clones made from a set of overlapping DNA fragments representing the entire genome of an organism. Compare *library.*

Genotype: The genetic constitution of an individual.

Germplasm: The total genetic variability, represented by germ cells or seeds, available to a particular population of organisms.

Germ cells: Egg and sperm cells and the cells that give rise to them.

GIFT : Gamete intrafallopian transfer, see above.

Gram-negative/positive: A classification of bacteria based on differential staining utilizing the Gram-Wiegert procedure. Primarily as a result of an organism's cell membrane structure, gram-negative organisms stain red and gram-positive organisms stain purple.

Gynecology: Branch of medicine dealing with diseases of the female reproductive tract.

Haploid: A single set of chromosomes (half the full set of genetic material), present in the egg and sperm cells of animals and in the pollen cells of plants. Human beings have 23 chromosomes in their reproductive cells. Compare *diploid.*

Health: A state of physical, mental and spiritual well-being.

Heterozygous: Having two different alleles at the same point on a pair of chromosomes.

Histocompatible: The condition in which tissues will not react to produce a rejection during transplantation.

HIV: Human immunodeficiency virus, a causative agent in the disease*AIDS.*

Homologous recombination: A process of DNA exchange where introduced DNA is substituted for native DNA containing identical or very similar (homologous) nucleotide base sequences at the edges of the exchanged regions.

Homologous sequence: Nucleic acid segments having an identical or nearly identical linear order of nucleotide base pairs.

Homology: Degree of relatedness in appearance, function, or structure.

Homozygous: Having identical alleles at the same point on a pair of chromosomes.

Homeo box: A short stretch of nucleotides whose sequence is virtually identical in all the genes that contain it. It has been found in many organisms, from fruit flies to human beings. It appears to determine when particular groups of genes are expressed in the development of the fuit fly.

Horizontal transfer: The passage of genetic material from one organism to another via nonsexual mechanisms.

Hormone: Chemical substances produced in one part of the body that affect an organ or group of cells in another area of the body.

HUGO: Human Genome Organisation, an international body to coordinate efforts to sequence the humane genome (see *human genome project*).

Human gene therapy: Insertion of normal DNA derectly into cells to correct a genetic defect.

Human Genome Initiative: Collective name for several projects begun in the mid 1980's in several countries, following the USA Department of Energy decision to 1) create an ordered set of DNA segments from known chromosomal locations, 2) develop new computational methods for analyzing genetic map and DNA sequence data, and 3) develop new techniques and instruments for detecting and analyzing DNA.

Hybridization: The process of joining two complementary strands of DNA, or of DNA and RNA, together to form a double-stranded molecule.

Hydatidiform mole: A placental abnormality composed of grape-like clusters of chorionic villi. It is the product of an abnormal fertilization where live placental tissue is formed without any embryo.

Hybridoma: A new cell resulting from the fusion of a particular type of immortal type of immortal tumor cell line, a myeloma, with an antibody-producing B lymphocyte. Cultures of such cells are capable of continuous growth and specific (i.e. monoclonal) antibody production.

Ice-minus (ice-): A bacterium lacking a functional gene coding for a protein that promotes the formation of ice crystals by providing a physical nucleus around which

ice crystallizes. The gene has been deleted from strains of Pseudomonas syringae Pseudomonas fluorescens, and Erwinia herbicola.

Ice-plus (ice+): A bacterium with an intact, functional ice-nucleating gene.

Immunodeficiency: The state of sub-standard expression of the immune system.

Immunosuppression: That state of inhibiting the expression of the immune system.

Imformatics: The study of the application of computer and statistical techniques to the management of information. In genome projects, informatics includes the development of methods to search databases quickly, to analyze DNA sequence information, and to predict protein sequence and structure from DNA sequence data.

Implantation: The process by which the fertilized oocyte (zygote) becomes attached to the wall of the uterus (endometrium). It commences in the seventh day or human embryo development, and is completed by day 14.

In vitro: Literally "in glass"; pertaining to a biological process or reaction taking place in an artificial environment, usually a loboratory.

In vitro fertilization (IVF): A technique of medically assisted conception (sometimes referred to as "testtube" fertilization) in which mature oocytes are removed from a woman's ovary and fertilized with sperm in a laboratory. See *embryo transfer.*.

In vivo: Literally "in the living"; pertaining to a biological process or reaction taking place in a living cell or organism.

Infertility: Inability of a couple to conceive after a long period (e.g. 12-24 months) of intercourse without contraception.

Intellectual property: That area of the law involving patents, copyrights, trademarks, trade secrets, and plant vairety protection.

International technology transfer: Movement of inventions and technical know-how across national borders.

Intrauterine device (IUD): Contraceptive device inserted through the cervix into the uterine cavity.

Introns: The DNA sequences interrupting the protein-coding sequences of a gene that are transcribed into mRNA but are cut out of the messsage before it is translated into protein. Compare *exons.*

Invention: An original device, contraption, or process developed after study and experiment. Genetically engineered animals, plants, and micro-organisms have been recognized as patentable forms of biological invention in the United States, but this is not always the case in other countires, especially where animals are concerned.

IVF: *in vitro* fertilization (see above).

Karyotype: A photomicrograph of an individual's chromosomes arranged in a standard format showing the number, size and shape of each chromosome; used in low-resolution physical mapping to correlate gross chromosomal abnormalities with the characteristics of specific diseases.

Laparoscopy: Direct visualization of the ovaries and the exterior of the fallopian tubes and uterus by means of a laparoscope (a long, narrow, illuminated instrument) introduced through a small surgical incision below the navel, to evaluate any abnormalities. Surgical procedures may also be performed using this method.

Legalism: The position that ethical action consists in strict conformity to law or rules; cf. antinomianism, rules of practice, situationalism.

Library: A collection of clones in no obvious order whose relationship can be established by physical mapping. Compare *genomic library.*

Linkage: The proximity of two or more markers (e.g., genes, RFLP markers) on a chromosome; the closer together the markers are, the lower the probability that they will be separated during meiosis and hence the greater the probability that they will be inherited together.

Locus: The position on a chromosome of a gene or other chromosome marker, and also the DNA at that position. Some restrict use of locus to regions of DNA that are expressed. See *gene expression* and *alleles.*

Marker: An identifiable physical location on a chromosome (e.g., restriction enzyme cutting site, gene, RFLP marker) whose inheritance can be monitored. Markers can be expressed regions of DNA (genes) or some segment of DNA with no known coding function but whose pattern of inheritance can be determined.

Maternal serum alpha-fetoprotein: A protein secreted during gestation used to predict fetal abnormalities such as spina bifida.

Meiosis: The process of two consecutive cell divisions in the diploid progenitors of sex cells. Meiosis results in four rather than two daughter cells, each with a haploid set of chromosomes.

Mendelian genetics: Classical method of observing inheritance of a trait(s) in the offspring of crosses between individuals differing in that trait(s); results in accordance with Mendel's laws.

Messenger RNA, mRNA: A class of RNA produced by transcribing the DNA sequence of a gene. The mRNA molecule carries messages specific to each of the 20 amino acids. Its role in protein synthesis is to transmit instructions from DNA sequences (in the nucleus of the cell) to the ribosomes (in the cytoplasm of the cell).

Metaphysical: The principles underlying a particular subject or system of beliefs.

Microinjection: A technique used for the insertion of genes from one cell into another cell, in which highly purified copies of a specific gene of interest are injected into a cell. Sopies of one specific gene of interest can be injected into a fertilized animal egg. The egg is then surgically implanted in a female animal's reproductive tract.

Microorganisms: Minute, microscopic, or submicroscopic living organisms (e.g. bacteria, mycoplasma, and viruses).

Mitosis: A type of cell division that produces daughter cells which have the same number of chromosomes as the originating cells.

Monoclonal antibodies: Identical antibodies that recognize a single specific antigen and are produced by a clone of specialized cells.

Morula (the Latin for mulberry): Once the proliferating cells from the fertilized egg compact, they appear at the 12-16 cell stage like a mulberry. Hence the name is applied to the embryo about three days after fertilization.

MRC: The Medical Research Council, for example of the United Kingdom.

Multifactorial or multigenic disorders: See *polygenic disorders.*

Mutagen: An agent (e.g. Ultraviolet light, X-rays, certain chemicals) that increases the frequency or extent of mutation.

Mutagenesis: A process that results in modification of a DNA sequence.

Mutation: Any change in DNA sequence that results in a new characteristic that can be inherited. Compare *polymorphism.*

Negative eugenics: Policies and programs intended to reduce the occurrence of

genetically determined disease.

Natural selection: The process of differential reproductive success by which genes in a population increase or decrease in frequency with the passage of generations, depending on their contribution to the survival of offspring in which they are carried; arguably the most important of the several mechanisms by which evolution takes place, discovered by Darwin and first described in 1858-59.

Neural tube defect: A condition resulting from the failure of the neural tube to close during fetal development, resulting in spina bifida or anencephely.

NIH: National Institutes of Health of the USA.

Nonmaleficence: The state of not doing harm or evil; compare *beneficence*.

Nontherapeutic: Something which does not serve the purposes of benefitting an individual patient.

Novelty: One of the criteria used in the evaluation of patent applications. The invention or discovery being evaluated must be new and must not have previously existed through the work of others in order to be accepted on the grounds of novelty.

Nucleic acid: A macromolecule composed of sequences of nucleotide bases, DNA or RNA.

Nucleotide: A subunit of DNA or RNA consisting of a nitrogenous base (adenine, guanine, thymine or cytosine in DNA; adenine, guanine, uracil or cytosine, in RNA), a phosphate molecule, and a sugar molecule (deoxyribose in DNA and ribose in RNA). Thousands of nucleotides are linked to form the DNA or RNA molecule. See *DNA, base pair, RNA.*

Nucleus: The membrane-enclosed structure in eukaryotes that contains the chromosomes.

Obstetrics: The branch of medicine dealing with the management of pregnancy and childbirth.

Obviousness: Obviousness is one of the criteria used in the evaluation of patent applications. Obviousness addresses the degree of difference between the invention being evaluated and that which is already known and available.

Oligonucleotide: A short section of DNA.

Oligospermia: Scarcity of sperm in the semen.

Oncogene: A gene, one or more forms of which is associated with cancer. Many oncogenes are involved, directly or indirectly, in controlling the rate of cell growth.

Ontological: Refers to actual existence in reality as distinct from in thought or in the imagination.

Oocyte: The immature female germ cell. It is called an ovum when it matures after the penetration of the sperm during fertilization and the completion of the second meiotic division.

Organelle: A structure in the cytoplasm of a cell that is specialized in its ultrastructure and biochemical composition to serve a particular function (e.g. mitochondria, endoplasmic reticulum, chloroplast).

OTA: Office of Technology Assessment of the USA.

Ovaries: Paired female sex glands in which ova are developed and stored and the hormones estrogen and progesterone are produced.

Oviduct: Fallopian tube.

Ovum (pl. ova): The female egg or oocyte, formed in an ovary.

Ovum donor: A woman who donates an ovum or ova to another woman.

Patent: A patent is a grant issued by different government through a Patent and Trademark Office that gives the patent owner the right to exclude all others from making, using, or selling a patented invention within the country for the term of the patent (e.g. in the USA this is for 17 years).

Paternalism: The system of action in which one person treats another the way a father treats a child, striving to promote the other's good even against the other's wishes.

Pathogenic: Able to cause disease; often utilized to express inactivation or lethality.

Phenotype: The characteristics of individuals which result from the interaction of their genotypes and their environments.

Physical map: A map of the locations of identifiable landmarks on DNA (e.g., restriction enzyme cutting sites, genes, RFLP markers), regardless of inheritance. Distance is measured in base pairs. For the human genome, the lowest-resolution physical map is the banding patterns of the 24 different chromosomes; the highest-resolution map would be the complete nucleotide sequence of the chromosomes.

Plant breeding: The development of plants with certain desirable characteristics, such as disease resistance.

Plant variety: Cultivated plants that are clearly distinguishable from others by one or more characteristics, and that when reproduced retain those distinguishing characteristics.

Plant variety protection: Patent-like protection for certain sexually produced plants. Plant variety protection is granted by many countries, and applies within those countries. It only applies if the holder ensures a reasonable commercial supply of that variety to all who want it.

Plasmid: An extrachromosomal, circular piece of DNA found in the cytoplasm and capable of replicating and segregating independently of the host chromosome. See *vector.*

Pleiotropic effect: The production of several unrelated changes in the characterisitics of a cell or organism by a single genetic change.

Polygenic disorders: Genetic disorders resulting from the combined action of alleles of more than one gene (e.g., heart disease, diabetes, and some cancers). Although such disorders are inherited, they depend on the simultaneous presence of several alleles, thus the hereditary patterns are usually more complex than those of single-gene disorders. Compare *singlegene disorders.*

Polymerase: An enzyme that assembles a number of similar or identical subunits into a macromolecule (e.g. DNA polymerase and RNA polymerase).

Polymorphism: Difference in DNA sequence among individuals. Genetic variations occurring in more than 1 percent of a population would be considered useful polymorphisms for genetic linkage analysis. Compare *muation.*

Polyploid: Having a chromosome number that is greater than two of the monoploid number. Polyploid oysters were among the first nonnaturally occurring, nunhuman, multicellular, living organisms to be declared patentable subject matter.

Positive eugenics: The achievement of systematic or planned genetic changes to improve indivicuals or their offspring.

Preembryo: The developing cells produced by the division of the zygote before the formation of the embryo proper at the appearance of the primitive streak. Also called pro-embryo.

Primer: A short piece of DNA that promotes DNA synthesis by providing a site for the action of the enzyme, DNA polymerase, to add nucleotides at one end of the primer.

Primitive streak: A pilling up of cells on the caudal end of the embryonic disc, providing the earliest evidence of the embryonic axis and the formation of the embryo proper. In human embryos this begins to occurs at about day 15.

Prior art: That which is already known or available, part of the criteria of obviousness used in evaluating patent applications.

Procaryote: Cell or organism lacking membrane bound, structurally discrete nucleus and subcellular compartments. Bacteria are examples. Compare *eucaryote.*

Protein: A large molecule composed of chains of smaller molecules (amino acids) in a specific sequence; the sequence is determined by the sequence of nucleotides in the gene coding for the protein. Proteins are required for the structure, function and regulation of the body's cells, tissues and organs, and each protein has a unique function. Examples are hormones, enzymes and antibodies.

Protoplast: A plant cell whose wall has been removed by enzymatic or mechanical means.

Recessive: A trait or condition which is only expressed in individuals who have two identical versions of a particular gene, one inherited from their mother, and one from their father.

Recombinant DNA: Hybrid DNA sequences assembled *in vitro* from different sources; or hybrid DNA sequences from the same source assembled *in vitro* in a novel configuration.

Recombinant DNA technologies: Procedures used to join together DNA segments in a cell-free system (an environment outside of a cell or organism). A recombinant DNA molecule can enter a cell and replicate there, either autonomously or after it has become integrated into a cellular chromosome.

Recombination: The formation of a new association of genetic material. It is usually applied to the process of meiosis, during a stage of which the genetic material packaged into gametes is mixed and reconstituted in any of an enormous number of possible combinations. It is also applied to genetic engineering.

Replication: The synthesis of new DNA strands from existing DNA. In human beings and other eukaryotes, replication occurs in the nucleus of the cell.

Resolution: Degree of molecular detail on a physical map of DNA, ranking from low to high.

Restriction enzyme, endonuclease: A protein that recognizes specific, short nucleotide sequences and cuts DNA at those sites. There are over 400 such enzymes in bacteria that recognize over 100 different DNA sequences. See *restrction enzyme cutting site.*

Restriction enzyme cutting site: A specific nucleotide sequence of DNA at which a restriction enzyme cuts the DNA. Some sites occur frequently in DNA, every several hundred base pairs, but others occur much less frequently, may be every 10,000 base pairs.

Retrovirus: A family of Viruses whose genetic material is RNA and is further characterized by the presence of reverse transcriptase in the virion.

Reverse transcriptase: An enzyme capable of directing the production of a simgle-strand DNA copy form an RNA template.

RFLP, restriction fragment length polymorphism: Variation in DNA

fragment sizes cut by restriction enzymes; polymorphic sequences that are responsible for RFLPs are used as markers on genetic linkage maps.

Ribosomal RNA, rRNA: A class of RNA found in the ribosomes of cells.

Risk: The probability of adverse effects, their nature, and their severity over a range of exposures.

Risk/Benefit: A decision-assiting process that attempts to identify, estimate and weigh all the risks and benefits associated with a particular action and to determine whether overall the benefit would be worth the associated risk.

RNA, ribonucleic acid: A chemical found in the nucleus and cytoplasm of cells; it plays an important role in protein synthesis and other chemical activities of the cell. The structure of RNA is similar to that of DNA. There are several classes of RNA molecules, including messenger RNA, transfer RNA, ribosomal RNA and other small RNAs, each serving a different purpose.

RU-486: The steriodal antiprogestin milepristone, which is capable of inducing early abortion by inhibiting the secretion of progesterone.

Safety: The reasonable certainty that no harm will result under expected conditions of use.

Schizophrenia: A psychotic disorder characterized by personality disintegration and distortion in the perception of reality.

Secular ethics: Theories of what is good and bad, or right or wrong, based on criteria other than religious doctrine.

Seed: A mature ovule, consisting of an embryonic plat together with a store of food, all surrounded by a protective coat. A seed usually develops following the fertilization of an egg cell by a male generative cell from a pollen grain.

Selective advantage: An organism's increased probability of reproduction and producing offspring, conferred by its genetic characteristics.

Selective pressure: The influence of factors extrinsic to an organism (i.e. environmental factors) on its ability to compete with other organisms for reproductive success.

Semen: A fluid consisting of secretions from the male's seminal vesicles, prostate, and from the glands adjacent to the urethra. Semen carries sperm and is ejaculated during intercourse.

Sex chromosomes: The X and Y chromosomes in human beings that determine the sex of an individual. Females have two X chromosomes in diploid cells; males have an X and a Y chromosome.

Sexual reproduction: Reproduction that occurs as a result of the interaction between the two sexes. In plants, sexual reproduction occurs when a female egg cell is fertilized by a male generative cell from a pollen grain. Examples of sexually reproduced plants are corn, wheat and sorghum.

Single-gene disorders: Hereditary disorders caused by a single gene (e.g., Duchenne muscular dystrophy, retinoblastoma, sickle cell disease). Compare *polygenic disorders*..

Site-directed mutagenesis: The modification of a DNA sequence at a location that is precisely controlled.

Situationalism: The position that ethical action must be judged in each situation guided by, but not directly determined by, rules.

Somatic cells: Any cells in the body except reproductive cells and their precursors.

Species: Taxonomic category subordinate to a genus composed of individuals with common characteristics that distinguish them from other groups of the same taxonomic level; in sexually reproducing organisms, a group of interbreeding natural populations that are genetically distinct from other such groups.

Species barrier: The idea that there is a natural barrier between species that preserves their integrity or identity. This idea has no known foundation in biology. The parameters that limit the ranges and variations of species are fluid and variable, and species exist as reproductive communities rather than as separate creatures.

Species integrity: The idea that a species has integrity as a biological unit. This would have to be based on the identity of the genetic material carried by the species. However, it is not clear how a species might be defined genetically, and this issue is the subject of debate among those seeking to understand the nature of species.

Sperm: The male reproductive cell, or gamete. Normal sperm have symmetrically oval heads, stout midsections, and long tapering tails.

Sperm bank: A place in which sperm are stored by cryopreservation for future use in artificial insemination.

Statute: Legislation enacted by a legislature.

Strain: A pure culture of organisms within a species, characterized by one or more particular physical or genetic properties.

Surrogate: Someone serving as a substitute decisionmaker.

Surrogate mother: A woman who is artificially inseminate, with sperm or embryo, and carries an embryo to term, with the intention of relinquishing the child at birth.

Syndrome: The combination of signs and symptoms which occur together in any particular disorder.

Syngamy: The mingling of the male and female haploid shromosome sets following the breakdown of the pronuclear membranes. This results in the formation of the zygote.

Syphilis: A sexually-transmitted disease caused by an organism called spirochete.

Technology transfer: The process of converting scientific knowledge into useful products.

Teleological: Explaining phenomena by their design, purpose, or final causes.

Teratogenic: Producing malformation in an embryo or fetus.

Teratoma: A new and uncontrolled growth of cells and tissues that are the product of an abnormal fertilization without any potential to develop into an embryo proper or fetus.

Therapy: The provision of remedies in the treatment of disorders or illnesses.

Tissue culture: The propagation of tissue removed from organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements.

Tissue plasminogen activator (tPA): A genetically engineered protein drug that helps to dissolve blood clots in patients who have suffered heart attacks.

Tort: A private or civil wrong resulting from a breach of a legal duty that exists by virtue of society's legal expectations regarding interpersonal conduct, rather than by virtue of a contractual agreement.

Totipotency: This represents the capacity (potential) of a cell or a cluster of cells to produce the whole (total) embryo and fetus with all its extraembryonic membranes and tissues. Pluripotency or multipotency is similar but is restricted to represent the

capacity to produce a variety of parts and tissues but not the whole embryo and fetus.

Toxicity testing: The use of experimental procedures to determine the levels at which exposure to a material leads to adverse effects in test subjects, the characterisation of such induced effects and the elucidation of mechanisms of action by which effects were induced.

Toxin: Most often, a toxic peptide or protein capable of eliciting antibody production. A toxicant is a substance that has been shown to present some significant degree of possible risk when consumed above safe limits by animals. See *endotoxin* and *exotoxin.*

Transcription: The synthesis of mRNA from a sequence of DNA (a gene); the first step in gene expression. Compare *translation.*

Transduction: The transfer of genetic material from one cell to another by means of a virus or bacteriophage.

Transfer RNA, tRNA: A class of RNA having structures with triplet nucleotide sequences that are complementary to the triplet nucleotide coding sequences of mRNA. The role of tRNAs in protein synthesis is to bond with amino acids and transfer them to the ribosomes, where proteins are synthesized according to the instructions carried by mRNA.

Transformation: Introduction and assimilation of DNA from one organism into another via uptake of naked DNA.

Transgenic animals: Animals whose hereditary DNA has been augmented by the addition of DNA from a source other than parental germplasm usually from another animal or a human, in a laboratory, using recombinant DNA techniques. At the moment, most of the research in this field is done on mice, but major research efforts in transgenic animal modification are also focusing on cattle, pigs, sheep, poultry, and fish.

Translation: The process in which the genetic code carried by mRNA directs the synthesis of proteins from amino acids. Compare *transcription.*

Translocation: The transfer of genetic material from one chromosome to another. An exchange of material between two chromosomes is referred to as a 'reciprocal translocation'.

Transposable element: A class of DNA sequences capable of insertion into a genome at numerous positions, and of moving from one area of a genome to another area or another genome.

Transposon: A type of transposable element incapable of autonomous existence, often shuttling genetic material back and forth between cell chromosomes, between smaller replicons, and between chromosomes and replicons.

Ultrasound: The use of high-frequency sound waves focused on the body to obtain a video image of internal tissues, organs and structures. Ultrasound is particularly useful for in utero examinations of a developing fetus, for evaluation of the development of ovarian follicles, and for the guided retrieval of oocytes for IVF and GIFT.

Unconstitutional: Conflicting with the provisions of a constitution, usually the U.S. Constitution. Statutory provisions or particular applications of a statutory provision found unconsitutional are thereby rendered void.

Utilitarian: The view that an action is deemed morally acceptable because it produces the greatest balance of good over evil taking into account all individuals

affected.

Utility: The state of being useful or producing good.

Utility patents: Usefulness or utility is one of the criteria used to evaluate patent applications. Utility patents are patents issed to inventors of any new and useful process, machine, manufacture, or composition or any new and useful improvement there of.

Vasectomy: Sterilization of a man by surgical excision of a part of the vas deferens.

Vector: DNA molecule originating from a virus, a bacterium, or the cell of a higher organism used to carry additional DNA base pairs; vectors introduce foreign DNA into host cells, where it can be reproduced in large quantities. Examples are plasmics, cosmids and yeast artificial chromosomes.

Virus: Any of a large group of organisms containing genetic material but unable to reproduce outside a host cell.

Wild-type: An organism isolated from nature.

X-linked: Genes carried on the X chromosome.

Zona pellucida: A thick, transparent noncellular layer of uniform thickness surrounding the oocyte, zygote and early embryo for several days, when it degenerates and allows the embryo to everge or hatch out.

Zygote: The fertilized egg; the single cell that is formed when the two haploid sets of chromosomes in the pronuclei of the male and female gametes come together at syngamy. Also used loosely to refer to the early embryo during the first few weeks.

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