Genetic engineering in New Zealand: science, ethics and public policy

Darryl Macer
Molecular Biologist and Bioethics Specialist
University of Tsukuba
Japan

Howard Bezar
Technology Transfer Scientist
DSIR Crop Research
Lincoln
New Zealand

Janet Gough
Risk Assessment Scientist
Centre for Resource Management
Lincoln University
New Zealand

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Lincoln University

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Executive summary

Genetic engineering is rapidly being acknowledged as an emerging technology that has immense potential to improve the health, living standards, economy and environment for New Zealanders. However, some aspects of the technology challenge social values, legal and environmental protection, and production systems.

This study was undertaken to present a balanced discussion document describing the science of and the social, ethical, commercial, safety, legal and environmental issues associated with genetic engineering.

Potential applications

For an economy dependent on quality food production and export, the potential for improved, 'cleaner, greener' plant and animal products is much improved by genetic engineering technologies. There is huge potential for improved human health through new methods for screening for disease, better therapeutic drugs, new vaccines and systems of therapy. For industry there will be new and more efficient industrial processes. There is also much potential for improved pollution control and replacement of environmentally harmful chemicals and production practices.

Local research

Genetic engineering research in New Zealand is advanced in international terms. As the economy is based upon biological industries this research should receive more support in New Zealand than may be appropriate in other countries. Research in many of the basic aspects of molecular biology is being undertaken in the universities with more applied work underway in plant and animal improvement in DSIR and MAF Technology (in many cases, collaboratively with universities). There is little private sector research. Although the research is concentrated on the agricultural applications of the technology there is an increasing level of research with potential industrial and medical applications.

Public opinion

New Zealand has some excellent up-to-date opinion survey information on public attitudes to genetic engineering and biotechnology. The public is aware of the benefits of genetic engineering but people also have some concerns, especially about research involving humans and animals. The principal concerns of New Zealanders involve the concept of "interfering with nature" and the risks associated with the research and the release of new organisms into the environment. The Maori perspective is in many ways similar to the stewardship role of environmentalists but they also have a deeply-held spiritual feeling for living things and the land.

Ethical issues

Since the first genetic engineering experiments, both scientists and the public have expressed concern about genetic engineering. Public concerns include fear of the unknown, concerns about scientists 'playing God', the question of interfering with nature, the integrity of species, the risk of unforeseen consequences, and the problems arising from the reduction of genetic diversity. Scientists themselves have been responsible for alerting the public about the risks but their concerns largely focus on the safety issues relating to the environment and food. Scientists argue that the findings of science are ethically neutral, but the practice of science is not. Therefore, universally agreed codes of ethics need to be developed that respect human life and the environment and the future of both.

Safety issues

Safety issues arise in several areas. Researchers can ensure that experiments are carried out under conditions that reduce the likelihood of organisms being released into the environment. Laboratory procedures are well established and in most countries codes of practice ensure that high standards of safety are met. The main concerns about field trials are connected with the spread and persistence of genetically-modified organisms (GMOs) and potential ecological effects. Of greater concern is the ease with which experimenters could ignore regulations and deliberately release organisms into the environment. Under these circumstances there is considerable uncertainty about the potentially harmful effects of such actions on the environment.

Risk management procedures provide a systematic approach to minimising accidental release, examining the effects of field trials and commercial application, and at the same time provide a means of tracking and guarding against malicious release.

Education issues

Public acceptance plays an important role in the determination of safety and, in the case of novel genetic technologies such as genetic engineering, education is required to raise the public's awareness and understanding of genetic engineering. The level of public debate on such issues would be improved if science teaching included coverage of risk and ethics.

Commercialisation

The commercialisation of products from genetic engineering is occurring rapidly and if progress is to be encouraged property rights that are within the bounds of public acceptance must be clarified. The patenting of life-forms and genetic material is clearly a contentious issue although the majority of New Zealanders support some form of property rights protection for animals and plants. There are a number of legal uncertainties about the scope and extent of patenting life-forms.

Policy issues

Public policy is concerned with the public good. Protecting the public interest requires legal structures and introduces the question of monitoring for the purpose of determining the risk to the public. There is a need to revise a number of regulations, establish some statutory controls, revise some intellectual property law, monitor some procedures, ensure our research is well planned and adequately resourced, establish a national bioethics committee and respond to public needs for information.

CHAPTER 1

Introduction

Genetic engineering is rapidly being acknowledged as an emerging technology that promises immense potential for improving the health, wealth and environment for human kind. With an economy dependent upon quality food production and export, New Zealanders are aware of the benefits of 'the new genetics' and yet they are also aware of the risks. New Zealanders have concerns because some of the new technology challenges existing social values, legal and environmental protection, and production systems.

The purpose of this study is to present a balanced New Zealand perspective on the issues; to describe the science, to discuss the ethical and social issues, to examine the safety and legal framework and to point to some policy issues that require further detailed analysis.

The subject is technically and politically complex and in order to merely summarise these issues this publication is longer than intended. We have focused our attention on those applications of genetic engineering that are associated with the commercial, ethical and environmental concerns of the community. There is also much basic research in genetic engineering and biotechnology that is important in every aspect of modern biology and is an integral part of current scientific and medical research.

We urge further debate of issues among the community. Academics, researchers, business, agriculture and medical professionals have a responsibility to assist in the provision of educational resources to facilitate that debate. Policy makers must respond by formulating effective policies to harness the potential of the technology while minimising adverse impacts on the environment.

> A simple definition: **genetic engineering** encompasses those techniques that manipulate DNA or genes to introduce, delete or enhance the genetic make-up of an organism. **Biotechnology** is any technique that uses living organisms or processes to make or modify products, the environment or organisms.

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CHAPTER 2

Applications of genetic engineering

"The $2 billion domestic biotechnology industry is expected to increase to $40 billion by the year 2000." Dan Quayle, Vice President USA, February 1991

2.1 DNA and genes: some technical background
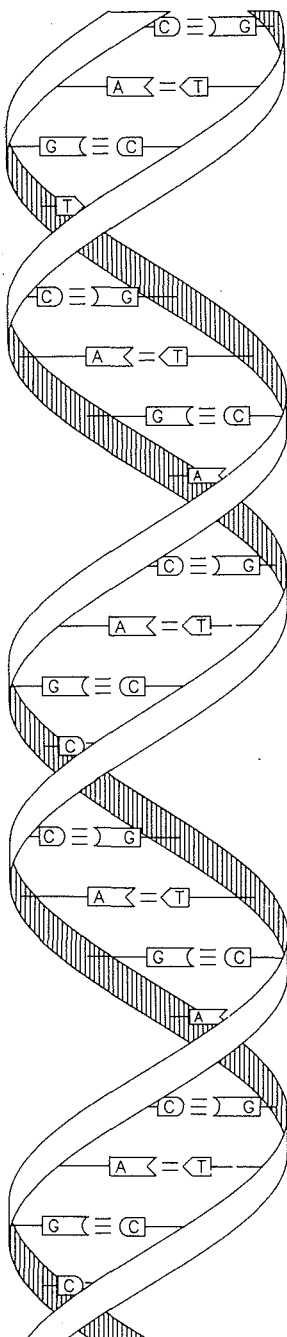
All living organisms are constructed of cells, the basic unit of life. Most cells can reproduce themselves although some organisms may contain living specialised cells that have lost this ability to multiply. The fundamental information that programs all cells is contained in the DNA (deoxyribonucleic acid) of the cell, which is its hereditary material. This essential information is organised into genes, therefore genes are composed of DNA.

Chemically, DNA is composed of four basic building blocks, called nucleotides. Informally these are also called bases. The four nucleotides are A (adenosine), G (guanosine), C (cytosine), and T (thymidine). In cells, the DNA carrying the hereditary information is actually composed of very long strands of the four bases, hooked together in a specific yet seemingly random order. The DNA strands pair together in the famous and now familiar 'double helix' form presented by James Watson and Francis Crick in 1953. This pairing of the DNA is held together by recognition between the bases: A pairs with T, and G pairs with C.

Each gene carries the instructions for a product needed by the cell or organism. When a cell 'reads' a gene, it follows a specific process:

$$DNA \rightarrow RNA \rightarrow PROTEIN$$
'transcription' 'translation'

Either RNA (ribonucleic acid) or protein can be the end-products of the process, however, specific proteins are the end-products for most genes. RNA and DNA are chemically similar, but protein is different since it is composed of combinations of 20 distinct amino acids.

Genes vary in length and therefore have an almost infinite ability to produce unique products. The average gene is about 1,000 bases long and makes a protein of about 300 amino acids.

The number of possible variations of the four bases to produce such a gene ($4^{1,000}$) is huge, a larger number than most pocket calculators can produce! In human beings there are estimated to be 30,000 to 100,000 genes and the longest one found to date is composed of 2,000,000 bases. With the technology of modern genetics and molecular biology, it is possible to determine the exact chemical sequence of any gene from any organism.

The genotype of an organism is the complete set of genes that it possesses. This is inherited from its parent or parents, whether the organism arose from asexual or sexual reproduction. Generally, the cells of an individual organism are the same genotype (i.e. the DNA is the same) if they arose from one single cell. Naturally occurring, deliberate rearrangements of the DNA of some cells in some organisms have been shown to occur, however. Accidental rearrangements of the DNA sequence can also occur and these are called mutations. For sexually reproducing organisms, the genotype of each new individual (brothers or sisters) is different because the genes from the parents are shuffled by a process called recombination.

2.2   The development of genetic technology

In 1967 an enzyme DNA-ligase was discovered which joined breaks in a DNA chain. The first artificial gene was made in 1972. Enzymes called restriction endonucleases were found in different bacteria that cut DNA at short, specific sequences of bases. This allows DNA to be precisely cut into smaller pieces. Selected pieces of DNA can also be joined together. These new pieces of DNA can be incorporated into carriers called vectors. The vector used for bacterial genetic engineering is usually a virus or plasmid that resides in bacterial cells. These viruses or plasmids normally multiply in the cell, and will also do so with any inserted foreign DNA. For insertion into cells of higher organisms the DNA is usually incorporated into the cell's chromosomal DNA. This may occur by use of an intermediate vector which normally inserts itself into the chromosome.

Between 1973 and 1976 scientists agreed to operate under a set of specific genetic technology guidelines for fear that moving genes widely could have bad consequences. For instance, it could aggravate the spread of antibiotic resistance, toxin formation, some genetic determinants for tumour formation, or human infectious diseases to bacterial populations, which in turn might have spread these genes to humans.

Now that scientists and legislators have resolved that such experiments are safe under certain conditions, the technology has been extended to increase greatly the number of different vectors, so that many organisms can be 'engineered'. The range of possibilities has also increased with the large number of different genes that have been identified, sequenced and isolated. Recombinant DNA technology could allow the earth's entire genetic resources to be exploited by providing a means of greatly accelerating natural gene transfer events. Some interspecific and inter-kingdom 'genetic engineering' has been occurring in nature for eons, without apparently catastrophic consequences. 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 antigenicity of proteins.

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2.3 Medical benefits

There are already many medical benefits generated by genetic engineering and the phenomenon will be the basis of an increasing proportion of medicine. Some examples are provided to give an idea of the broad range of applications.

2.3.1 Human proteins made in micro-organisms

Micro-organisms have been used during the last 50 years to produce medically important drugs such as antibiotics. During the late 1970s genes that direct the synthesis of mammalian proteins including human genes were inserted into bacteria. The bacteria can be grown in large cultures to produce vast quantities of medically important proteins. 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 in bacteria, yeast and eucaryotic cell culture. These proteins include blood clotting factor VIII, interferons, interleukins, growth hormone, erythroprotein, insulin, tissue plasminogen activator and various growth factors, all of which have medical uses.

These proteins can be used to treat patients that lack these hormones or enzymes, or they can be used to treat other diseases such as cancer. By the end of 1990 there were only 10 of these proteins licensed in the USA (and other countries), but 104 await approval from human trials. It is estimated that by the year 2000 about 50% of all approved drugs will be made using these recombinant DNA techniques.

2.3.2 Animals and plants produce human proteins

Animals have been genetically modified to produce desired proteins in their milk. To date, mice and sheep have successfully been used to make the human blood-clotting factor for the treatment of haemophilia, as well as the protein alpha-1-antitrypsin which can be used to treat emphysema, a lung disorder caused by a deficiency of this protein. There are advantages in using plants and animals rather than bacteria for producing proteins as they make a protein identical to human proteins. The mammary gland is very useful because, for example, in sheep about 400 litres of milk can be collected per lactation cycle (in cattle the figure is 8,0007 litres). Rabbits are also being used. Another advantage is that the cost of producing a herd of animals is much less than the cost of an industrial-style factory using bacteria, and it could be used in developing countries to boost economic development.

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. Silkworm caterpillars have been used to produce human insulin and human serum albumin has been produced in potato and tobacco plants. However, this research serves mainly to illustrate a potential. It has not yet approached commercialisation.

2.3.3   Vaccines

Human and animal vaccines are being made using recombinant DNA techniques. A vaccine against Hepatitis B has already been approved for worldwide use. There has been much research on the molecular basis of these diseases which will hopefully allow the development of vaccines for malaria, AIDS, hepatitis A, B, C, polio and other major diseases. There have also been vaccines developed against animal diseases such as foot and mouth, sheep foot rot, rabies, rhinderpest, or tapeworms. Multiple disease resistance using single application vaccines is a realistic target for the 1990s.

2.3.4   Genetic screening

Every human being has a different set of genes, or genotype. Sexual reproduction is a risky business, with a relatively high occurrence of abnormalities. Many of these are aborted naturally, however, 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. In 10% of these the protein abnormality has been defined. There are numerous other multiple gene disorders, and much is still unknown about the association between genes and health or disease. There are also many chromosomal aberrations where there are unusual numbers of chromosomes. Genetic probes can be sequenced and used for screening.

Currently, the major application of genetic screening is in pre-natal screening. It is now possible to take a sample of the chorionic villi (membranes around the fetus) at 12 weeks and analyse the fetal DNA directly to determine whether it has a specific genetic defect. The older technique, amniocentesis, is performed at 12-16 weeks of pregnancy. Both techniques have a 0.5 to 1.5% risk of miscarriage due to the procedure. We are still unable economically, ethically, or socially, to screen every fetus for many diseases with these techniques. They are currently used only for screening fetuses from parents who want to use it and have a high risk of genetic disease. If, in the future, cheap multiple screening techniques become available, routine screening will be more widespread.

During 1988 a major revolution in genetic techniques occurred, with the capacity to analyse DNA from a single cell using the DNA Polymerase chain reaction (PCR). In this technique, the single original copy of DNA is multiplied thousands of times by the technique, allowing DNA to be identified, within four to six hours. The technique is of very broad use in genetic analysis. If used after chorionic villi only very small samples are required allowing screening to be performed at earlier stages in pregnancy.

A new method is available for genetic screening of embryos. Embryos (within one week after conception) can be genetically screened before implantation. Pre-implantation screening only began in 1989 and is still being developed. The first births were of female babies, selected by the absence of the Y-chromosome for sex-linked genetic disease. Currently few laboratories have skills in embryo manipulation, and *in vitro* fertilisation has a low success rate.

Genetic screening is also used on adults, and poses some ethical problems. For example people who have a parent suffering from Huntington's disease are at 50% risk that they will also suffer this debilitating disease soon after they become 40 years old. Young adults (generally children are not offered this screening) can undergo a genetic test, which will tell them whether they have the disease-causing allele of the gene. Such testing is called pre-symptomatic testing, because it is testing before there are any symptoms of the disease. It is further complicated when medical

insurance is desired because insurance companies may require genetic screening to minimise risk. In the USA this occurs for an increasing number of diseases for which tests are available. Such tests have also been used by employers to reject job applicants. There are many different applications of genetic screening. Applications for medical reasons are generally accepted, but there is considerable doubt among many people about its use for commercial reasons which may impinge on personal liberties.

Recently a gene that codes for a protein p53, and other related genes, has been reported to be associated with different types of familial cancer.

2.3.5   DNA fingerprinting

DNA fingerprinting compares individuals on the basis of their DNA sequences. Each individual has a unique DNA sequence with about half of each DNA fingerprint inherited from each parent. Comparison of the parent's and child's DNA fingerprints can reveal the true genetic relationships. The evidence is accepted in many countries for criminal cases, in disputed paternity cases and for immigration purposes etc. It can also be used for tissue transplantation matching. Forensic science has begun to study small samples of blood or semen from criminal cases to match up DNA patterns with suspects. The samples can be amplified using the PCR technique described above, so that minute samples may suffice if they are not contaminated.

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 to cause changes in DNA, which means careful 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. In Europe there is a standardised technique, using the same restriction endonuclease (HinfI) and two standard chemical probes for DNA identification. The scientific basis of these applications is well established, but the practice has been found poor in cases where laboratory standards are not high.

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 this decade when the techniques have been standardised. It may certainly aid forensic science but it must be used according to strict guidelines to prevent the abuse of privacy.

2.3.6   The human genome project

The gene sequences of over 5,000 human genes, and the location of about 2,000 genes to areas of specific chromosomes are known. However, the total number of human genes is thought to be between 50,000 and 100,000. Moreover this compromises only 5-10% of the total DNA in the human genome. The aim of the genome project is to map and then to sequence all this DNA. The genome sequences will provide a method for tracing the history of molecular evolution as since fossil DNA sequences can be compared to current day sequences.

The US portion (possibly 50%) of the international project set up to complete this task is estimated at US$3 billion over the next 10-15 years. There are also multi million dollar projects underway in Europe and Japan. When one compares this with the cost of the development of a single drug, at US$50-100 million, or the annual US health care expenditure of over US$600 billion, some consider it is a small price to pay for such a large amount of information. The information gained will be the basis of much medical care in the next century. However, the gene sequences must be deciphered before they can be used in genetic screening and therapy. The first target of genome sequencing is to sequence all expressed genes by the year 2000. After these are sequenced, the rest of the DNA (95%) should only take five years to sequence because of automation.

2.3.7   Gene therapy

Due to recent rapid advances in molecular genetics it is now possible for the initial application of the technique of gene therapy to be undertaken; defective genes are substituted for correct genes. There are two levels at which this can occur, and they differ in the consequences they have for the patient. The genes can be inserted into specific cells of the body where the defect is causing the disease. This is called somatic cell gene therapy. 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 tissue. The other level of gene therapy, germline therapy, is discussed later in this chapter. Research in many laboratories over the last decade has been directed at developing safe and effective gene vectors for gene therapy use.

The first approved human experiments have begun in the USA using the technique of somatic cell gene insertion. The first trial, in 1989, 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 that attack cancer, called tumour-infiltrating lymphocytes (TILs). They are isolated from the patient's own tumour, then grown in large numbers *in vitro*. The cells are then given back to the patient, and stimulated using a naturally-occurring hormone, interleukin-2. The procedure is known to help about half 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 10 patients, but this number was increased following the success of some of the preliminary group of patients. More recently, approval was given in France for a similar technique to be used on 10 patients suffering from an incurable skin melanoma.

A trial involving the insertion of the gene for tumour necrosis factor in TILs, which will be conducted in 50 patients with advanced melanoma, passed the final stages of approval in August 1990. 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 that will kill the tumour, and then die. Other trials have also been approved in the USA and in Europe for a rare immune deficiency (ADA deficiency), and a growing number of trials have been approved. By mid-1991 patients had expressed the inserted ADA gene, and their immune systems are becoming functional for the first time.

By mid-1991 approval had been given for protocols involving the introduction of novel genetic elements that may confer drug resistance to normal bone marrow cells and allow their survival during cancer chemotherapy. Gene therapy is another medical tool to help individuals overcome an illness, and somatic cell therapy raises no fundamentally new ethical problems compared with existing treatments.

The other class of gene therapy is called germline gene therapy, where the gene is inserted into the sperm or eggs, or early embryo, to replace the defective gene. Because the gene would be heritable by future generations, most governments have limited all gene therapy experiments to somatic cells. This restriction has been imposed until the public has had sufficient time to decide if germline gene experiments are desirable restriction has been imposed and on what kinds of disease.

2.4   Agricultural applications

For millennia plants and animals have been selectively bred to develop varieties that are more productive. The welfare of humanity is inextricably bound up with efficient agriculture. Genetic diversity is limited within a species so the search for diversity has led breeders to use new genetic technology. Conventional breeding is limited to sexual crosses and is slow and costly. Recombinant DNA technology breaks down inter-species barriers and makes very novel genetic combinations possible.

2.4.1   Genetically-modified plants
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* to transfer genes. 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 with their cell walls removed) from which plants can be regenerated. 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 with DNA on their surfaces. During 1990, researchers produced fertile genetically-modified rice, maize and sorghum, which are all very important as food crops. This makes more useful and widespread applications of GMOs imminent.

Plant disease resistance
About one third of total crop losses are directly attributable to plant disease. Viruses cause serious diseases in many crops. The genetic basis of viral resistance in plants is narrow, so strains of virus that are beyond resistance of plants frequently appear. Isolating the plant's own resistance genes to combat disease is not practical until the genes have been identified. The function of such genes depends on complex factors, such as the right genetic background. However, good viral disease control via genetic engineering has been obtained using several approaches. The technology works and the goals are now to obtain multiple viral resistance, and to extend the work to different plants and viruses.

Pest-resistant plants
There are many problems associated with pesticide use, including pest resistance to chemicals and negative environmental effects. Some biological control methods are being used, but increasingly export markets require pesticides to be used to satisfy their quarantine standards. The production of pest-resistant plants by genetic engineering will help reduce pesticide use.

Plants expressing an insecticidal protein of a bacterium, *Bacillus thuringiensis*, known as Bt proteins, can be resistant to attack by most caterpillars. There are slightly different naturally occurring types of this Bt protein that are specific to different species of insect. These different types can be used

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separately or in combination to make plants resistant to more insects. The Bt protein gene has been put into crop plants including corn, cotton, soybean, tobacco and tomato, to reduce damage from insect larvae. The control of caterpillar pests with plants expressing this insecticidal gene offers several advantages. Control is independent of the weather. All parts of the plant can be protected but in some cases it may be preferable not to express the protein in edible parts of the plant. However, there is some concern about the development of resistance to Bt proteins.

> The major corn seed producer, Pioneer Hi-Bred International, has joined the farming trend to recommend a switch to the use of Bt as a pest control agent instead of chemical pesticides. Many US farmers are using biocontrol agents, including pheromones to upset pest mating as well as Bt, viruses and fungi. Subspecies of Bt have different activities, which has limited its use as a general pesticide. Recent interest in Bt protein has been boosted by reductions in its production costs. Developments in genetic engineering are likely to broaden the specificity of the proteins.

An alternative way of controlling herbivorous insect pests is by introducing genes for protease inhibitors into plants, so that the pests digest food with reduced efficiency. The expression of these genes, which are thought to be a defensive response to insect attack, can be enhanced. They have an effect on a wide range of insects and have a low level of human toxicity.

Herbicide tolerance and weed control
Genes that give plants tolerance to herbicides have been isolated and incorporated into some plants. Work has concentrated on herbicides that are more environmentally friendly than those commonly used. Plants resistant to the herbicides Roundup, Glean, Oust, and Basta have been made. Research has mainly been conducted on those herbicides with properties such as high unit activity, low toxicity, low soil mobility, rapid biodegradation and with broad spectrum activity against various weeds. The development of crop plants that are more tolerant to such herbicides should provide more effective, less costly and more environmentally attractive weed control.

There are several advantages of herbicide-tolerant plants. Herbicide-tolerant plants will reduce overall herbicide use and also substitute for more effective and environmentally acceptable products. Their obvious use is in removing weeds from crops. Herbicide-resistance can also be used to maintain genetic purity during seed multiplication of new cultivars. It could allow chemical thinning of crops after the mixing of parent and resistant seeds and 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. There is some debate about the commercial motives used in developing these plants, that will be discussed later, but until we have a much better knowledge of biological control, these plants will have many applications.

Food
The most obvious improvement accomplished by traditional breeding is increased yield. Genetic engineering techniques have the potential to increase yield, as they complement the traditional technology. Yield is no longer the only goal; improving the quality and marketing appeal of food

and using genetically-engineered pest and disease resistance to produce healthier products are also goals.

The food content of seeds and plant products can be altered to improve their nutritional and post-harvest qualities. One approach involves using antisense RNA sequences to bind to the mRNAs of undesired proteins and reduce the concentrations of enzymes. This technique has been applied to tomatoes to reduce the level of the enzyme polygalacturonase, which is produced by ripening tomatoes and causes softening of the tomato. The concentration of this enzyme was reduced by 99%, so the fruit stay firm. These tomatoes have been developed to improve shelf life and taste since growers can leave the tomatoes on the plant longer for natural ripening. These tomatoes will be available when confirmed safe for human consumption, probably by the end of 1992 in the USA.

Forestry
Genetic engineering research for forestry species is generally lagging behind that for agriculture and horticultural species for several reasons. For most tree species, breeders have only reached the second or third generation of improvement. The generation time is also very long, with about 15 years required between generations. There is still a large amount of natural variation available in tree populations, and tree breeders have not seen a need for genetic engineering to improve traits such as growth rate, tree form, disease resistance and wood properties. However, genetic engineering may have a role in improving traits that are difficult or impossible by conventional tree breeding. These include disease and insect resistance, herbicide resistance, male sterility, and wood properties such as lignin and natural preservatives. Progress has been made, especially with hardwoods, where *Agrobacterium* can be used as a vector. Herbicide resistance in *Populus* species provides an example. The ballistic gun has shown promise with coniferous species, and successful transformation has been demonstrated using marker genes such as kanamycin or GUS.

Ornamental plants
There have also been advances in the breeding of ornamental plants. The choice of flower colour has the potential to be extended, as novelty is added, such as rare blues or purples. More long term objectives involve altering flower morphology and improving vase life. Productivity will also be improved, as with other plants, by incorporating disease and pest resistance. Genetically-engineered roses, carnations, chrysanthemums and gerberas, with different leaves, petals, stem lengths and colours are immediate goals. Unlike foodstuffs, there will not need to be proof that these products are safe for human consumption but they will still require approval for field release.

2.4.2   Extending animal breeding
Genetic alteration can be used to improve weight gain, disease resistance and fertility in farm animals. In the past, animal breeders have had to rely on the opportune use of stud animals that have the desired qualities in selected mating using natural or artificial insemination or in vitro fertilisation (IVF) and embryo transfer. Farm animals will continue to be bred using existing methods of gene transfer and artificial insemination or embryo transfer, but will require help from bioengineering to improve fertility and reduce disease.

Field testing of transgenic cows, pigs and sheep is already underway. The term 'transgenic' was first applied to a mouse strain that had foreign genes integrated into its genome in 1981. The enhanced

growth of mice after transfer of a growth hormone gene is being repeated in other animals, most effectively in fish. There are transgenic rabbits, sheep, pigs and cows, but the animals do not grow much faster. The first pigs that were tested, were found to grow up to 20% more rapidly, but had a high morbidity. The ability to produce pigs exhibiting only the beneficial side of growth hormone gene expression, increased weight gain and less fat, was developed in some British experiments. They have inserted the gene so that it can be turned on or off by a chemical trigger placed in the feed to control the amount of fat on transgenic animals.

It is a common misconception that genetic engineering will increase the size of animals. In most cases smaller animals are desired as they are cheaper to maintain. What is desired is rapid growth rate, or turnover. This also means that the average age of farm animals will decrease - a trend that has been occurring because younger animals are more efficient, such as egg-laying hens or dairy cattle. Besides increasing growth rate, other agricultural aims include decreasing water dependence and increasing drug resistance and disease resistance. Some of the effects may be less controversial 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. Dairy cows in the 1980s produce 2.5 times more milk than those in the 1940s, for example. Genetic engineering thus has the capacity to change dramatically the metabolic characteristics of animals and hence may have a dramatic effect on the industry.

In addition to improving growth rate, a major target of genetic engineering in sheep is to improve wool production. 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 by increasing sulphur amino acids, in the forage.

There have been attempts to make chickens resistant to common viruses by transforming developing chick embryos. Salmonella resistance would help to avoid the use of antibiotics, which cause problems when they are passed on to human consumers.

Fish are more easily genetically manipulated using current techniques because natural fertilisation of eggs is external, and there are numerous large eggs that make microinjection relatively easy. Genes of immediate usefulness that are already available in fish are the growth hormone genes, globin genes, 'antifreeze' genes, 'disease resistance' genes and 'digestive enzyme' genes. The initial projects are aimed at improving the growth rate in commercially important fish species.

2.5 Environmental applications

Genetic engineering has potential to improve our environment. Many applications will replace older and more harmful techniques and result in reduced pollution and more rational use of non-renewable resources. There have been, and are, many future possible uses of micro-organisms in the environment, and this range has been greatly expanded by genetic engineering. Bacteria and viruses have been used as pesticides to kill mosquitoes that cause malaria or to prevent wheat from diseases during silo storage, to avoid using other pesticides. Increasing consumer pressure and environmental concerns are forcing a switch from chemical pesticides to biological control (Chapter 2.4.1).

Antibodies could be used to scavenge small organic pollutants, such as toxins, from the environment if they can be produced cheaply in plants, as previously described (Chapter 2.3.2). Bacteria can be used to chelate toxic compounds, such as heavy metals, and to remove organic compounds, phosphorus, ammonia or other pollutants by bio-conversion. During the Exxon Valdez oil spill in Alaska in 1988, a 1989 oil spill in the Gulf of Mexico in Texas, and in the Gulf oil spill in 1991 bacteria were used to degrade oil with limited success. This option was particularly important in the low temperature Alaskan environment where oil degrades very slowly. A mixture of oil-degrading bacteria, which are sometimes selected from those naturally mutated at polluted sites, and fertilisers to make them grow, are applied together to the oil-polluted beaches or open sea.

> The fatty acids in the membranes of cells determine how the plants respond to environmental stress, so by altering the fatty acids in the membranes environmental tolerance can be varied, for example, to lower or higher temperature extremes. Plants may thus be rendered more resistant to drought, flooding, salinity and heavy metals, and can be grown in regions beyond the tolerance range of species, or even areas unable to be used for agriculture at all. About 30% of the world's land area has conditions that create major plant stress, including insufficient soil nutrients or water, or toxic excesses of minerals and salts. Tolerance to low temperature may also be important. The antifreeze gene from an arctic fish has been transferred to soybean with the goal of creating plants tolerant to low temperature.

A major long term project for crop improvement is to characterise, then transfer, the genes for nitrogen fixation into non-leguminous plants to enable them to fix atmospheric nitrogen to save using nitrogen fertilisers. However, the nitrogen-fixing pathway involves 17 different genes and their interrelationships are important. 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'. Another approach, and some scientists believe a more realistic one, would be to manipulate nitrogen-fixing microbes to produce nitrogen in otherwise non-leguminous plants rather than transferring genes to plants.

2.6   Industrial applications

Micro-organisms, because of their size, life habits and versatility have long been used to produce both simple chemicals and complex brews. In the last decade the long history of human use of micro-organisms has been extended as genetically-engineered bacteria and yeasts have become commonly used. Bacteria are also currently used in metal leaching for mining.

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 high concentration of 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 speeding up chemical reactions and are more tolerant to extremes of temperature during industrial processes. Genes are being isolated from thermophilic bacteria and transferred to other organisms. This will allow thermophilic enzymes to be produced more easily for fermentation and other industrial applications.

Enzymes are the catalysts that carry out all the synthetic and degradative reactions of living organisms. One everyday example of a genetically-engineered product is that of 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'.

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 with synthetic polymers, with the advantage of biodegradability to avoid pollution problems. New types of products, like synthetic rubbers, are objectives of this research. Bacteria can also be made to produce the raw material for biodegradable plastic bags. This would also avoid using nonrenewable and energy intensive production techniques.

Transgenic plants are 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. There have also been pharmaceutical peptides produced in oilseed rape plants. Some of these proteins could be economically produced in the seeds of plants. The genes for biopolymer production may be put into foodcrops such as potato tubers because potatoes produce a high biomass per unit area in a wide range of environments. Potatoes are already used for starch biosynthesis and their long natural storage characteristics make them equally suitable for use in bipolymer production.

CHAPTER 3

New Zealand research

"Scientists are rarely the heroes in the current world of popular culture." George
Basalla, 1976

Genetic engineering research in New Zealand began in about 1974, the same time as overseas, but increased considerably in the mid 1980s. There has been a history of basic research on other novel genetic techniques and tissue culture which contribute to the foundation for much of the current research. By the early 1970s there were several areas of basic research at the Universities of Auckland and Otago (molecular biology), Waikato University (thermophile enzymes) and DSIR Palmerston North (protoplast fusion). It was some of this latter work of Dr Ken Giles on the fusion of *Azotobacter* and mycorrhizal fungi, which live on *Pinus radiata* roots, that led to some concerns about the safety of such work. Some of these plants were suspected to have died from a possible 'new' pathogen, however the cause was more likely to have been a natural pathogen. The Advisory Committee on Novel Genetic Techniques (ACNGT) grew out of the need for guidelines for recombinant DNA work. Research on genetic engineering expanded rapidly through the 1980s and began to move from largely basic research to research that had economic objectives. In the late 1980s the government provided impetus to the research with the allocation of 'new policy' funding to DSIR to expand this research.

During the mid 1980s the principal aim was to establish the skills and facilities for inserting genes into plants based on technology imported from overseas. Work began on the developing techniques for inserting genes into cells of plant species of particular New Zealand significance, and regenerating plants from the transformed cells. These species included white clover, kiwifruit, potatoes and asparagus. The major genes available at the time were marker genes (genes that can be easily detected but are of no economic use) such as kanamycin resistance and also genes for tolerance to herbicides. Considerable progress was made during this period in the development of the technology and the first field trials of a GMO, a potato, took place in the summer of 1988/89.

A significant level of recombinant DNA research throughout government departments and universities in New Zealand forms the basis of our understanding of genes and their mode of action in this country. More recently there has been a significant amount of research done in mapping genes in sheep, apples and peas, and in cloning genes that may be of use in plant and animal breeding.

3.1   Plant improvement

In Table 3.1 the major projects being undertaken in New Zealand involving genetic engineering are summarised. The larger part of this work can be categorised as plant improvement.

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The effect of virus diseases in plants is often poorly understood as some crops are rarely free of virus. In recent years, substantial improvements in crop quality and yield have been obtained through pathogen testing techniques which enable virus disease to be substantially reduced. For example, in garlic pathogen-tested seed yields about 80% higher yield and a higher proportion of export-grade bulbs. Thus, plant virus resistance is a major aim for many crops in which viruses are known to cause significant economic loss. Viral resistance can be obtained by taking a coat protein gene from the virus and inserting it into the affected plant. The mechanism for this protection is not well understood but it appears to be an effective 'vaccination' against the virus. Virus resistance is being sought in potatoes, tamarillo, white clover, peas and brassica crops.

Table 3.1   New Zealand plant genetic engineering.

A. Genes being cloned for plant breeding

Antirrhinum gene for use in modifying flower colour	MAFTech/DSIR Chemistry
virus coat protein genes to confer resistance to viral disease including: potato virus X potato virus Y potato leafroll virus pea seed borne mosaic virus white clover mosaic virus alfalfa mosaic virus beet western yellows virus tamarillo mosaic virus	DSIR Plant Protection DSIR Crop Research DSIR Crop Research DSIR Crop Research DSIR Plant Protection DSIR Plant Protection DSIR Plant Protection DSIR Plant Protection University of Auckland
Bacillus thuringensis genes coding for proteins toxic to a range of insect pests, leading to the development of insect-resistant crops	DSIR Plant Protection
a number of enzyme inhibitors useful for the development of insect-resistant crops	DSIR Fruit and Trees DSIR Grasslands DSIR Plant Protection
aluminium tolerance to overcome limits to agricultural production on acid soils	University of Auckland MAFTech
alinase, a gene for onion flavour production	DSIR Crop Research
genes affecting apple ripening and storage characteristics	DSIR Fruit and Trees
genes affecting kiwifruit ripening characteristics	University of Auckland DSIR Fruit and Trees
genes for disease resistance and male sterility in important forestry species	Forest Research Inst. Fletcher Challenge Ltd
cloning and expression of genes involved in bacterial plasmid replication	University of Auckland

B. Transfer systems for inserting genes into the following plants

peas, onions, brassicas, asparagus, potatoes, lettuce, lentils and chickpeas	DSIR Crop Research
tamarillo, pepino, kiwifruit, apples, sweet pea	DSIR Fruit and Trees University of Auckland
white clover, perennial ryegrass, lucerne	DSIR Grasslands
geranium, lisianthus, chrysanthemum, petunia	MAFTech, Levin
gene promoters from agronomically and horticulturally useful plants	University of Otago DSIR Fruit and Trees

C. Foreign genes are being inserted into the following plants

geranium, lisianthus chrysanthemum, petunia	altering flower colour	MAFTech, Levin
white clover	expression of a sulphur-rich seed storage gene to increase wool production	DSIR Grasslands CSIRO (Aust.)
white clover	insect resistance using potato proteinase inhibitor II and Bt gene	DSIR Grasslands
white clover	herbicide resistance	DSIR Grasslands
white clover	resistance to the white clover mosaic virus	DSIR Grasslands DSIR Plant Protection
peas, lentils & chickpeas	virus resistance	DSIR Crop Research
brassicas	pest and disease resistance	DSIR Crop Research
potatoes	for the production of thaumatin (a sweet protein) as an industrial product	University of Canterbury
kiwifruit and apples	insect resistance using Bt genes	DSIR Fruit and Trees University of Auckland DSIR Plant Protection
potatoes	pest and disease resistance	DSIR Crop Research
asparagus	resistance to the herbicide, Roundup	DSIR Crop Research
strawberries rockmelon	increased sweetness using the thaumatin gene	University of Canterbury
plants	for the production of pharmaceutical products	Lincoln University

Pest resistance is also of increasing importance to industries that must meet difficult pesticide residue standards for export crops. One of the most important developments genetic engineering is likely to make is to provide the technology to confer natural genetic resistance to pests where none previously existed. The main methods being used in New Zealand to improve pest resistance involve the insertion of *B. thuringensis* genes, which confer resistance to lepidoptera (caterpillar) and coleoptera (beetle larvae) species, or inserting protease (enzyme) inhibitor genes from other plants or animals, which protect against insect and microbe attack.

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Herbicide tolerance in plants has been important as a model system for New Zealand researchers and may result in some economic benefits. Field trials of potatoes resistant to the herbicide 'Glean' have been undertaken but transformation of the potentially more useful Roundup-resistant asparagus has proved to be more difficult to achieve. A white clover resistant to herbicide will soon be made and could be of major benefit to seed growers by enabling them to eradicate volunteer clover plants.

Plant tolerance to stress is an important aspect of plant adaptation to the environment. Aluminium toxicity is a problem in many low pH soils, especially in the high country of the South Island. Work is underway at Auckland University and MAF Technology to improve resistance to high levels of aluminium and overcome some of the limits to agricultural production.

Alteration of the protein composition of plants has the potential to lead to many advances in better quality food products. The gene for pea albumin is being transferred to white clover to improve the sulphur-rich proteins that are important for wool production in sheep. Other advances in food quality such as improved nutritional value of grain legumes and wheat breadmaking quality are dependent upon successful manipulation of seed storage proteins.

A range of other genetic engineering work involving the colour of flowers and fruit, the flavour of onions, fruit ripening, storage quality and the size and variety of a range of fruit is being investigated.

3.2   Industrial developments

Industrial uses of GMOs have been recognised for some time and research on enzymes from thermophilic bacteria pioneered at Waikato University, has been particularly successful. Other work on the modification of yeasts and bacteria used in the dairy industry is underway. Industrial agriculture is an area in which the new technology could yield great economic potential to New Zealand. The use of microbes, plants or animals to produce highly valuable industrial or pharmaceutical products will expand worldwide. Given New Zealand's agricultural background we are well placed to play an important role in industrial developments made possible by genetic engineering (Table 3.2).

Work initiated at Canterbury University on the transfer of the thaumatin gene provides a useful example of the potential for industrial developments. The commercial production of thaumatin, a sweet protein from *Thaumatococcus danielli*, a rare West African plant, has considerable potential as a low calorie sweetener if it can be transferred to a high biomass crop such as potatoes and easily extracted in sufficient quantities.

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Table 3.2 New Zealand microbial genetic engineering.

A. Microbial genes cloned or being cloned

yeast	a *Candida albicans* exo-glucanase gene	University of Otago
yeast	*Schizosaccharomyces* genes for malate utilisation	Massey University
bacteria	*Lactococcus lactis* genes for use in the dairy industry	Massey University NZ Dairy Research Institute
fungus	gene transfer and gene replacement systems in the perennial ryegrass endophyte, *Acremonium lolii*	Massey University
bacteria	Rhizobium genes for nitrogen fixation	DSIR Grasslands
bacteria	Rhizobium genes involved in nodulation and infection	Massey University
bacteria	Agrobacterium genes for plant-microbe interactions	DSIR Grasslands
bacteria	thermophilic enzymes	University of Auckland
bacteria	*Clostridium acetobutylicum*	Massey University

B. Foreign genes being inserted into microbes

E. coli (bacteria)	insertion of a gene that produces an enzyme useful in the food processing industry	DSIR Industrial Processing
bacteria	altered genes for biosensor development	DSIR Grasslands
bacteria	genes from *Clostridium acetobutylicum* for alternative fuels from farm and forestry waste	University of Otago
virus	rotavirus gene into baculovirus expression vector	University of Auckland DSIR Plant Protection DSIR Ind. Processing
baker's yeast	allowing the yeast to grow on whey	Lincoln University

3.3 Animal research

The principal animal research in New Zealand is being conducted by MAF Technology at Ruakura and Wallaceville, Massey University, Lincoln University and a University of Otago/MAF Technology group. Research includes the development of animal vaccines, the production of pharmaceutical products in mammalian milk and techniques for producing transgenic sheep (Table 3.3).

Table 3.3 New Zealand animal genetic engineering.

A. Genes cloned for animal improvement and systems for gene transfer

A major programme aimed at detecting and isolating sheep genes associated with production characteristics i.e. reproduction, disease resistance, wool growth.	University of Otago MAF Technology
isolation of genes from deer relevant to disease resistance and growth	University of Otago MAF Technology
DNA probes for *Mycobacterium paratuberculosis* and Giardia	Massey University
isolation and modification of lactoferrin genes	Massey University
isolation of genes involved in sheep muscle development	MAF Technology University of Auckland
isolation of sheep insulin-like growth factor cDNA clones	University of Otago

B.   Foreign genes being inserted into animals

sheep	to assess the potential for gene expression in the wool follicle	Lincoln University
mice	for basic studies of gene expression and as models for human disease	Lincoln University
mice	to study DNA elements that enhance transgenic expression	MAF Technology Ruakura
mice	to study the control of bovine milk gene expression	MAF Technology Ruakura

3.4   Environmental applications

Although there is little research directly targeted at environmental protection in New Zealand (see Section 2.5), a number of areas of research will have beneficial environmental effects. Introducing herbicide-resistant genes into crops, such as the introduction of the Roundup-tolerance gene into asparagus, is aimed at replacing the use of toxic chemicals (in this case diquat and paraquat) with safer herbicides. Most of the research on disease and pest control will also have important environmental benefits. Some preliminary work has been done on the possibility of transferring genes from bacteria that are antagonistic to fungi into plants susceptible to fungal attack. The conservation, in its natural habitat, of the rare African plant that produces thaumatin could be an added benefit of the work being undertaken on the thaumatin gene.

Table 3.4 Environmental applications.

virus	genes from hepatitis A, human rotavirus and *E. coli* for water quality monitoring	University of Otago

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3.5 Medical genetics

Knowledge of gene sequences and techniques for their clinical use are rapidly expanding in New Zealand. Already several hospitals are screening for genetic disorders. There are no theoretical limits to the use of these techniques providing they are in accordance with the existing therapeutic goals of medical genetics, perhaps with the exception of limited facilities and trained personnel. The shortage of trained genetic counsellors will delay the use of these techniques more than anything else. There is potential for abuse of genetic screening in employment and life insurance situations but there are substantial therapeutic benefits in their use. The only genetic screening underway in New Zealand is for diseases that are specifically found in higher frequency among New Zealanders. This screening includes identifying some diseases or disease susceptibilities found in higher frequency among Maoris and other Polynesians.

New Zealand researchers can be expected to play only a small role in the human genome project, but it is still in New Zealand's best interests to contribute something, as the USA has warned that data will be withheld from those countries that do not contribute anything to the project. This may seem unethical, but it is an unfortunate fact of the commercial nature of the international genome project, and one that should not be ignored. In spite of the reservations of some scientists about this project our best avenue of contribution may be to analyse the structure and functions of individual genes as this will be a limiting factor.

Associated with the genome project is the large growth in commercially available genetic screening tests that will be imported from overseas. This will have benefits for New Zealand. These screening tests, however, cannot screen everyone because of the individual variation in gene sequences, therefore the facilities for analysing individual mutations will need to be retained and developed. New Zealand researchers have done some internationally recognised research on specific genetic diseases, and if this clinical and research base can be built on, then New Zealand may still be able to contribute enough information to continue to be a recipient of the information contributed from overseas researchers.

3.6 New Zealand field trials of genetically-modified organisms

Regulation of the release of GMOs in New Zealand is based on the case-by-case assessment of proposals by the Interim Assessment Group (IAG) which is serviced by the Ministry for the Environment. A background paper on the New Zealand situation was published in February 1987 by the field release working party. After circulating a draft document public submissions were received. Most favoured the establishment of a statutory committee that would make it obligatory for all proposals for the release of a GMO to be notified. At the time of writing the committee is still without a statutory basis, but is functioning until one is established. The IAG currently has an advisory role. By agreement between the Minister for the Environment and all other departmental Ministers, researchers in the public sector are obliged to submit all proposals to field test or to release GMOs in New Zealand to the IAG for its advice. Private researchers are also encouraged to follow these obligations. The IAG's 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.

Table 3.5 Genes being cloned for disease diagnosis and prevention.

human	genes involved in cancer	University of Otago
human	genes involved in genetic disease e.g. muscular dystrophy	University of Otago
human	genes involved in immunity	University of Otago
viruses	genes of dengue virus for vaccine development	University of Otago
viruses	genes of orf virus for vaccine development	University of Otago
viruses	Rotavirus vaccine production by genetic engineering routes e.g. high expression of Rotavirus antigens in Baculovirus vectors	University of Auckland
bacterial	cell wall protein genes from Streptococcus spp. that cause sore throats and heart disease	University of Otago
bacterial	Pseudomonas aeruginosa genes involved in causing disease	University of Otago
bacterial	genes from Lactobacillus reuteri to understand infectious disease processes	University of Otago
bacterial	bacteriocin genes from bacteria that are involved in tooth decay	University of Otago
bacterial	genes for the control of protein synthesis in bacteria	University of Otago
bacterial	expression of Mycobacterium leprae and M. tuberculosis proteins in mouse antigen-presenting cells	University of Auckland
yeast	enzyme genes from the disease-causing yeast Candida albicans	University of Otago
various	insulin-like genes for diabetes and other cell function research	University of Otago

Since 1988 the IAG has considered 24 applications for work with GMOs including field testing, transport and export. From DSIR there have been two applications for large scale fermentation, 10 involving potatoes, one asparagus, one broccoli and one for baculovirus export. From MAF Technology there has been one application for testing Aujeszky's disease vaccine, 1 for transporting mice, one for a sheep spermatozoa vector, and three for ornamental plants. From Canterbury University there have been two applications for potato taste panel trials. From Coopers Animal Health there was an application for large scale fermentation work. Strict conditions are imposed, for example where field plots of a species of potato are grown they are isolated from other crops of the same species. The experimental site is monitored for pollen dispersal from the transgenic plants and for the appearance of volunteer plants in subsequent growing seasons.

As indicated, there are a number of projects being developed in New Zealand that will lead to applications for field trials. The legislation governing GMOs was intended to be part of the Government's Resource Management Bill however the intention, at the time of writing, is to establish a Commission under separate legislation that will assume responsibility for all phases of genetic engineering research.

CHAPTER 4

Public concerns

"Scientists are transferring genes across species barriers that have been erected by centuries of evolution. This frightens many people. They worry about the possibility of affecting the voluntary process itself, and whether human beings have the wisdom to do so intelligently." D. Habar, 1989

4.1 Public attitudes to science

Public attitude to science is important, particularly in New Zealand where most science is publicly funded. The consequences of scientific research will be felt by the public and in contentious areas, such as genetic engineering, public attitudes become more important. Adverse opinion, even a minority opinion, can result in protest action that may result in entrenched adverse opinion based on emotional responses. Scientists have been warned that they need to encourage well informed public debate on genetic engineering issues, and in some New Zealand towns this has occurred.

In mid-1989 public attitudes to the broader issues were probed in the UK and Australia. The results to some key questions are interesting, and were largely 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 each?", of the British public 44% thought more good, and nine percent more harm, and of the Australian public 56% thought more good and 10% more harm. In Britain 74% agreed that many of the world's problems can be solved by scientific research, whilst in Australia 65% were of this opinion. Seventy-six per cent of the British and 63% of Australians thought that national prosperity depended on science and technology (Kenward 1989). Biennial surveys are also conducted for the US National Science Board and have consistently portrayed strongly favourable attitudes towards science. These also suggest that the public can distinguish between science and the adverse effects of certain technologies.

In mid-1990 a survey of the attitudes of the New Zealand public to science and biotechnology found that 75% stated that they were interested in science and technology. These results together with media viewing and reading habit data suggest that the public has a good image of the use of science. Among farmers in the survey there was a significantly higher interest in science and technology. This public interest in scientific progress will help to facilitate and continue biotechnology and genetic engineering research. 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.

In the US survey, the public were also asked how much risk individuals thought would come to them or their families from science and technology; 22% thought a lot of risk, and 49% some risk. Asked how much benefit they saw coming from science, 41% said a lot, and 39% some. They were then

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asked if they thought the benefits will outweigh 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. People can entertain thoughts of both benefit and risk from the same technology, and genetic engineering is a good example.

4.2 Public attitudes to genetic engineering

4.2.1 Overseas

During the last decade there has been 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 realistic measurement of opinion. Face-to-face, non-leading questions with open responses are the best method but they are also more expensive than telephone polling. Since debate began in the 1970s, public opinion has turned to favour the use of genetic engineering techniques, within limits.

When people hear of the use of genetic engineering there are a variety of immediate reactions. In public opinion surveys some of these opinions were exposed. 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 said they know what DNA is, 42% thought that the rules covering genetic engineering were too slack.

In a 1987 poll of the US 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, although 55% thought that the risks of genetic engineering had been exaggerated. This was despite their lack of knowledge about the techniques involved. The survey found that while the public is concerned about genetic engineering in the abstract, most people approve of nearly every specific environmental or therapeutic application suggested in the poll. Asked "If there was no direct risk to humans and only remote risks to the environment would you 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 one in 1000, 55% would still approve if the product would significantly improve farm production. While members of the public can respond to such questions, their ability to make estimates of statistical risk is very difficult to gauge, and therefore they can only be relied upon to support general statements.

An independent survey was conducted by the Japanese magazine *Newton* (1989), a popular science magazine with a circulation of 300,000. They picked 500 people from their readers with a weighting towards people living outside large cities to get a different bias. The readers of this magazine are interested in science and technology; it is a selected sample rather than a public survey but is still useful. The results showed that 98% knew the word 'biotechnology', and 70% were interested in it, with most being a little interested. The survey showed that 77% were worried about the dangers

of biotechnology, and over half thought that they could not trust the researchers. Twenty-five percent supported protesters who were opposed to P4- and P3-contained laboratories in cities. Eighty-eight per cent thought that researchers would hide bad results or dangers from the public. The results of this survey are worrying in that it was conducted among people of a higher than usual science knowledge.

In 1990 a public opinion survey was conducted in Europe, by Gallup. It was based on samples of 1,048, 1,001, 605 and 512 adults in the UK, France, Germany and Italy respectively. Sixty-three per cent believed biotechnology will 'make life better', but 13% believed that biotechnology will make life worse and four percent wanted a total ban. People were concerned about a variety of dangers; 31% were concerned about eugenics, 27% about environmental harm and 17% were concerned about health hazards. The perceived benefits seen by 55% were cures for disease, and 22% thought that a principal benefit was reduced dependence on pesticides and chemical fertilisers. About one-third thought that biotechnology was ethical, 20% thought it was not, and the rest did not know.

4.2.2 New Zealand

As there has been no public debate of genetic engineering in New Zealand the only information on public concerns comes from the mid-1990 survey of the attitudes of New Zealanders to biotechnology conducted by Couchman and Fink-Jensen. The results of the face-to-face interviews are probably the most thorough and interesting poll information to date. People were asked for their awareness of different scientific terms and whether they could explain them to a friend. The results of this question are present in Table 4.1

Table 4.1 Results of New Zealand Public Attitudes Survey showing awareness of different techniques (Couchman and 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

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).

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The people who had heard of these techniques were also asked whether they thought these different areas were of benefit to New Zealand. The percentage of people who thought these techniques were worthwhile were: biological pest control 86%, silicon chips 62%, biotechnology 72%, fibre optics 66%, agricultural pesticides 85%, in vitro fertilisation 71%, superconductors 58%. For genetic engineering 57% thought research is beneficial, while 28% considered there would be few benefits.

This result suggests that there is a relatively low level of appreciation of the benefits of genetic engineering techniques to countries that have agriculturally-based economies like New Zealand. There were significantly fewer benefits seen to arise from genetic engineering among those with less education.

Those people who responded that they had heard of the individual techniques were asked how worried they were about the impacts of those techniques. They were asked whether they were not worried at all, slightly worried, somewhat worried, very worried or extremely worried about these techniques. The percentage of people who were at least slightly worried about these techniques was: 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 apparently benign 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. Among those with an undergraduate degree 73% expressed concerns, and 80% of those with a postgraduate degree expressed concerns. This may indicate that among the higher educated, the concept of genetic engineering is still not well understood. However, 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. This level of concern is balanced by an acknowledgment of the benefits. Most people accepted that the benefits outweighed the risks.

The survey showed that farmers were more aware of the technology and the perceived benefits of biotechnology and genetic engineering than the general public. However, farmers did show a similar level of concern to the public about developments in biotechnology

Teachers and scientists showed a much higher level of awareness of biotechnology and genetic engineering than the public or farmers and both teachers and scientists had a lower level of concern than the general public.

Another particularly interesting result from this survey is the perception of different aspects of genetic engineering. People were asked about their awareness of genetic manipulation in different areas. 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. Care was taken not to prompt respondents. These answers make interesting reading and have been summarised in Table 4.2. The concerns are similar to those indicated in surveys from other countries. The "unnatural" argument, although weak philosophically, is the most important reason given overall and will be discussed in Chapter 5. The fear of the unknown is also a concern and must be addressed by adequate safety precautions and will be addressed in Chapter 6.

Table 4.2 Attitudes of New Zealanders to genetic manipulation in different organisms, from sample of 2,034 adults (Couchman and 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	59	30	31
Heard only	40	29	44	43
Could explain	25	12	26	26
Which, if any, of these areas are unacceptable for any reasons?				
Acceptable	43	71	85	56
Unacceptable	58	29	15	44
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	52	37	13	34
Benefits	48	63	88	66
What benefits?	% who included as reasons:			
Cure disease	22	14	0	16
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

A substantial number of people did not think genetic manipulation of humans, plants, microbes and animals was acceptable. The reasons why they did not varied with the subject of the manipulation. Moral or ethical objections were expressed by 16% of the people who thought human genetic manipulation was unacceptable, and by 35% of those opposed to animal genetic manipulation. The low number of people who expressed moral disagreement with human genetic manipulation is surprising. However, there were other reasons for their objections.

Some of these concerns are usually expressed because of a misunderstanding of what is involved. Although people may understand the concept of genetic engineering very few people are aware of the nature of DNA. There is a need to clarify these objections to see why people raise them. Improved information may lessen some concerns, such as the fear of the unknown or interference with nature, but it may raise awareness of more important considerations in the use of genetic engineering.

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 than the public and they had greater interest in science than the public (Couchman and 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 public. However, their concerns about genetic manipulation in different organisms were not different to the public at large (see Table 4.3). Teachers and scientists were generally less concerned at genetic manipulation among all organisms than were other groups.

In the American OTA survey in 1987, 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. Forty-two percent said it was morally wrong, and 52% thought it was not. Given more specific applications, they were generally more supportive, such as to stop children from inheriting a usually fatal disease, 51% approved, and 33% somewhat approved, while only 15% disapproved. In the New Zealand survey the question about genetic manipulation was open and contrasted different organisms. The open question allows more analysis of people's reasoning for support, or 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 such as those in Germany (1935-45). 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 possibly because they were more aware of the therapeutic benefits. The comparative results are presented in Table 4.3. The results of both surveys suggest a mixed opinion over the use of human genetic engineering, especially if for medical reasons.

Genetic engineering was seen to be a more worthwhile area of research for New Zealand by scientists, farmers and science teachers than by the general public. This may be because the benefits more directly affect these groups, as they have a greater knowledge of the potential benefits. However, scientists also expressed concerns about genetic manipulation. The reasons for their concerns were different and included a greater weight on the ethics of such techniques, and the lack of controls on experiments, or the misuse of knowledge. This represents a different emphasis to the public. The fear of the unknown was still common, as were concerns about interfering with nature. These results suggest that genetic engineering is not well understood by any particular group.

Table 4.3 Acceptability of different areas of genetic manipulation by different groups within New Zealand public. The survey of the public was face-to-face, biology teachers, farmers and scientists were mail questionnaires (Couchman and 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	Occupation of respondents			
Manipulation in	Public	Teachers	Farmers	Scientists
Total No. in survey	2,034	277	200	258
Human cells				
Heard of (No.)	1,318	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 (%)	71.1	72.2	64.6	75.2
Unacceptable (%)	28.9	27.8	35.4	24.8
Plants				
Heard of (No.)	1,429	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.)	1,400	244	150	217
Acceptable (%)	56.4	81.6	65.3	77.4
Unacceptable (%)	43.6	18.4	34.7	22.6

4.2.3 The Maori perspective

Another view that contrasts with that of science is the Maori cultural perspective. There are three aspects of the Maori perspective that are pertinent to understanding the Maori response to European science. Firstly, there is the importance of spiritual values to Maori culture. The natural environment is seen by Maori as having both spiritual and physical dimensions, and all things are seen as having a spirit or 'wairua'. The second perspective is that of living in harmony with nature, with a deeply-held spiritual feeling for the land ('whenua') and an appreciation of the natural environment. This philosophy was expressed by the Waitangi Tribunal as follows:

"The natural world of the Maori is not divided into seen and unseen parts, but the physical and spiritual dimensions formed an integral and indivisible entity. That perspective dominates from the beginning and provides the foundation for later controls. Our world about us parallels our attitudes generally. Through occupation of Aotearoa we have developed an intimate relationship with our environment which emphasises the primacy of nature and the need for humans to tread carefully when interfering with natural laws and processes." (Waitangi Tribunal, 1985. Manakau Harbour Claim)

The third aspect of the Maori view, and intimately related to the other two aspects, is the notion of stewardship, fundamentally for 'whenua' (the land) but also for the well-being of the environment; it is on this stewardship that the mana of the tangata whenua depends. Important in this context are the rights granted to the Maori under the Treaty of Waitangi. According to the Maori translation of the original English text by Professor Kawharu (see Royal Commission on Social Policy, 1987), under Article 2 Maori are guaranteed "... unqualified exercise of their chieftainship over their lands, villages and all their treasures ('taonga')". It is in the latter area of 'taonga', which includes indigenous species regarded as precious, where problems can arise for genetic engineering. The concern of Maori is the risk (spiritual and physical) that is presented to their taonga by the introduction of GMOs. The view expressed by the Huakina Development Trust in 1988 is that it is critical that we know what effect these species would have on our taonga if let loose in the environment. The need for environmental impact reports on GMOs to include the effects on the indigenous flora and fauna was called for.

A clash of Maori and scientific world views was seen at the Ethnobotany Hui at Te Rehua Marae (Christchurch) in March 1988. One of the outcomes of the Hui was a recommendation that DSIR cease all experimentation relating to native plants and that there be no further registrations of native plant varieties under the Plant Variety Rights Act, at least until DSIR has completed a thorough consultation with the tangata whenua concerning their wishes about the uses of native plants. The Ministry for the Environment arranged a Hui to discuss the issue of new organisms in New Zealand at Maketu Marae (Kawhia) in December 1988. The main conclusions from this hui were that:

- there was a need for scientists to share information so that the public is better informed and can therefore participate more effectively in discussions
- there was a need for scientists to accept the 'validity of the Maori scientific perspective'
- any new legislation covering the introduction of new organisms should ensure that environmental impact assessments include consideration of the effect of the proposed introduction on Maori cultural values and taonga
- there should be significant Maori involvement in any advisory groups set up under regulatory legislation.

CHAPTER 5

Ethical issues

"Genetic engineering is a catalyst for bioethics." Daryl Macer, 1991

5.1 Fear of the unknown

The New Zealand survey found that the fear of the unknown was the fourth most common reason (Table 4.2) why New Zealanders found genetic manipulation unacceptable. About 8-11% cited this reason for genetic manipulation of humans, animals and plants, with a higher proportion (but lower number), 16%, citing it as a reason for the unacceptability of microbial genetic manipulation.

The nature of science is such that total consequences cannot be foreseen. We can guard against the risks that we can foresee; those we cannot foresee, we cannot guard against. The more rapidly we make changes to organisms, the less time we have to see the long term consequences of those changes. The question is whether we have the necessary knowledge and wisdom to alter successfully life-forms without creating long term and catastrophic eco-disasters. This is one of the major reasons why extensive 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. Only practical knowledge from controlled experiments can answer this question. It will be discussed in Chapter 6. It is also the reason why all new medical treatments undergo extensive clinical trials. New technology is rapidly taken up if it is better than old technology, but there will be situations where we do not use it because of unknown or unethical applications.

The experience of the last 15 year's 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, and cautious field testing regulations are in effect in many countries including New Zealand.

5.2 '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 behaviour is seen as being a demonstration of pride or arrogance. It is not the use of power and creativity that is wrong, but rather attributing power to our own resources. What is wrong is not the act itself, but the human-centred 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.

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The expression 'Playing God' 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 fundamental as genes.

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.

A further aspect is that of the concept of stewardship of the earth balanced with the creativity of man to find new technology to improve human health and the environment. Unfortunately, we often forget, or are ignorant of harmful environmental consequences of our technology. Now more is known we should use technology wisely and in a manner consistent with the concept 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 work. We should consider our knowledge when introducing any new variety of organism, however it was made.

5.3 Interfering with nature

There are also non-theological ethical objections to genetic engineering, as expressed by such statements as "we should not interfere with nature/natural evolution/the natural order of life". This 'meddling' is judged to be morally wrong, although not necessarily on religious grounds (although the same idea is common to people from many religious and cultural backgrounds). These objections were the strongest raised in the New Zealand survey and were strongest in relation to plant and human genetic engineering. Underlying the debate is unease about scientists digging around in the 'very stuff of life', in the heritable programmes which define us as individual humans. Many people believe that we are acquiring powers that humans ought not to have.

Interference with nature was cited as an objection by 33% when human genetic manipulation was involved, 22% for animal, 22% for microbial, and 35% were opposed on these grounds to plant genetic manipulation. There are a number of 'non-interventionalist', 'sanctity of life' objections to genetic engineering, that we should not interfere with nature as 'nature knows best'. However, we need only to think of the many diseases that afflict humans or other living organisms to put this idea in perspective. 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 we have developed.

5.3.1   Integrity of species
Scientists are transferring genes across species barriers that have been erected by millions of years of evolution. This frightens many people. Concern exists over the involvement of humans with the evolutionary process in a more direct way than is currently occurring. The level of concern in the New Zealand survey was low and often expressed within the concepts of possibility for disaster or creating mutants.

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However, modern biologists generally think of species as reproductive communities or populations. The species are limited by an arbitrary limit to variation. One species may exchange little or no genetic material with related or adjacent species, while another may seem to be almost promiscuous, interbreeding frequently with a neighbouring, related species. 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 that may contain 100,000 genes. There are objections also to 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. To challenge the integrity of a species requires more than a single gene change.

Perhaps, the greatest public concern is over the mixing of human and animal genes. Since much transgenic animal research is aimed at increased understanding of human diseases, the insertion of human genes may become common. The primary reason for this is convenience since 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.

5.3.2   Reducing genetic diversity

Uniform crop varieties are economically useful. Having a field of wheat that grows to the same height, producing good heads of grain that can be harvested at the same time, that 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 over a long period in Europe. Genetic variability that has been relied on for plant breeding is being lost. The value of gene banks should be consequently recognised.

There is the objection that cloning or tissue culture plant propagation will reduce the genetic diversity of a species. This would only apply if a significant proportion of the breeding population was developed asexually. We should always try to maintain diverse organisms, as such organisms tend to be better able, as a population, to survive major diseases or environmental changes. Modern breeders should realise the need to maintain stocks of the original species and the importance of maintaining a 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 - a calamity that has happened in the past for some organisms. New genetic techniques are actually being used to save the remaining genetic diversity, and will enable the practical use of many widely dispersed genes. The techniques of biotechnology should also aid the safe storage and regeneration of such germ-plasm. Another positive use of technology is to use common species as surrogate mothers to gestate the embryo of a rarer species using embryo transfer techniques and *in vitro* fertilisation rather than genetic engineering in the scientific sense.

The most powerful influence of genetic engineering will be indirect and should increase biological diversity. Because the efficiency of agriculture is increased, it is possible that large areas of land may be left fallow, allowing wildplants, such as wildflowers, to grow.

5.3.3   Sustainable agriculture

An important aspect of the debate about genetic engineering is that there are other world views that stress harmony between the human species and nature or that adopt a philosophy of fatalistic submission to the forces of nature. From the 1960s there has been a growing cynicism among people about science and technology. Up to the 1960s in the advanced industrialised nations there was a largely unquestionable acceptance of the beneficial nature of 'advances' in science and technology, since then there has been increasing concern about the social costs and dislocations of this 'progress'.

Central to the organic philosophy is a sense of living in harmony with nature; a philosophy illustrated by the concept of environmental stewardship. Ignoring this tenet and seeking to manipulate the environment through the methods of scientific agriculture, for example, is seen as unacceptable. Conventional agriculture, according to this perspective, is seen to be one that employs inappropriate and environmentally-unacceptable methods (which in the long term are not sustainable). Modern agriculture is seen as trying to produce a product that is non-sustainable or unsuitable for a particular environment, for example, trying to grow a sheep in an environment for which it is not correctly adapted. By contrast, the organic approach seeks to create production systems with low levels of inputs and interventions. Given these views, some who espouse an organic philosophy reject genetic engineering methods as trying to prop up a system that is failing. It is seen as a band-aid approach; there may be immediate apparent benefit, but it is not fixing the fundamental problem. From a New Zealand perspective, these views are seen by others as more appropriate to Northern Hemisphere conditions. Our approach to agriculture has been more sustainable than that of others and genetic engineering may help it become even more so.

Sustainable agriculture could be defined as the appropriate use of crop and livestock systems and agricultural inputs supporting those activities that maintain economic and social viability, while preserving the high productivity and quality of the land for future generations. Current research interests in biotechnology may not be the best way to provide sustainable agriculture. Large corporations are developing new products that may require constant, or at least annual, application. There has been little research into more long term controls, and cynics claim that this is because the companies will make more money out of repeated application products.

Herbicide-tolerant plants may not greatly reduce the amount of chemicals used, although this is denied by the companies producing them. One of Monsanto's projects is to develop soybean 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. While there are valid criticisms about the development of herbicide-tolerant plants, they do have immediate environmental advantages. For example, maize growers make four to six 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 a biodegradable herbicide could be used. Reducing herbicide use and switching to biodegradable products is consistent with sustainable agriculture and is an important practical step in that direction.

To determine what effect herbicide-tolerant plants will have on herbicide use, further study needs to be done. A project is underway at DSIR Crop Research Division in part funded by the Ministry for the Environment to investigate herbicide tolerance. Questions about public funding of herbicide-

tolerant crop development need to be asked. Research aimed at growing crops without herbicides and chemicals is needed, but it is a longer term goal and New Zealand will also benefit from herbicide-tolerant plants. Alternatives such as increasing the tolerance of crops to mechanical cultivation need to be investigated.

One hundred years from now the earth will probably have 10 billion humans, about twice its current population. Efficiency of food production must expand in a way that does not destroy the natural environment. 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. 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.

5.4 Slippery slopes

The concept of slippery slopes implies 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 that are adequate for initial exploration may fail under increased pressure. The argument is that if we alter the genes of plants, microbes and animals, then we will proceed 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 but the concern is valid. However, we should be sure that our society does stop extrapolation of this kind.

The New Zealand survey indicated some concerns in this area related mainly to animals and humans. However, the concerns were low in comparison with concerns about 'meddling with nature' and moral concerns.

The worldwide opinion of scientists, philosophers and legislators has turned to be supportive of many genetic technology applications. There is the principle of individual liberty to be upheld - 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, 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.

5.4.1   Eugenics
Of the many fears about the future abuse of science, the most sensitive areas are the changes that affect the inner constitution of humans. People express most concern about human genetic manipulation. The eugenic excesses of the Nazis and other countries in the first half of this century, must not be forgotten. Medical ethics should protect human beings from such blatant abuses, but

there are many other trends that we must remain alert to. For readers who seek more information on this, they are referred to *Shaping genes*. Genetics will be applied in increasing ways to human beings, as previously discussed.

The point at which we stop using gene therapy may be when it is no longer a treatment for a disease, but becomes enhancement. This problem emerges not only when we use genetic therapy, but is also found in common practice, 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 our understanding of human dignity we should stop using it, just as in other applications.

Many 'minor' diseases that are currently considered as grounds for selective abortion, do not seem to be sufficient to justify the use of abortion. In this category are included those diseases that are currently treatable and curable by medicine (e.g. some types of haemophilia), and other diseases such as albinism that are regarded simply as undesirable. Sex selection or other non-disease selection is considered to be unethical by most people. It is better for society to change than to mould birth control to please the current desires of some members of society, which may be based on prejudicial views.

To examine the alternatives it is important to look at the goal of genetic engineering. From the parents' perspective, it is aimed at producing a healthy child. At an individual level it is aimed at leading 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 at all levels. 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. In the case of recessive genetic diseases, it will be possible to select those embryos that do not have the disease-causing genes, implanting only those that 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 unthought of technological development.

There have been objections to human cloning, which is not allowed in most western countries. The major objection is that the clone may gain some defect as a result of the cloning process. The objections to germline gene therapy could be applied equally to attempts at human cloning; splitting an embryo could be considered genetic manipulation. There are clauses in the laws of most countries that permit human embryo research in order 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 pre-implantation diagnosis, and the possibility for future genetic therapy that cures disease.

5.4.2 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. This research is already a reality; it is difficult to stop but, like a nuclear holocaust, its use can be prevented. New Zealanders prevent such research occurring in New Zealand. The fear of biological warfare is not an argument for stopping research in other areas of genetic engineering, which promise many benefits.

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. 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.

5.5 Animal rights

We may all agree that animals can suffer. There may be a choice between human welfare and the suffering of nonhuman animals. One of the most important criteria in judging the use of animals by humans is that of avoiding the infliction of pain. The capacity for suffering and/or enjoyment has been described as a prerequisite for having any interests. 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. Some animal rights activists reject these principles, such as Peter Singer who 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". 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.

5.5.1 Making new strains of animals

Historically, mankind has developed new breeds of animals that display specific characteristics. Most of these animals have been for agricultural use, but recently some have been bred for biomedical research. Genetically-engineered animals are becoming the preferred source of experimental animals. Scientists prefer to use standardised animal strains for experiments, and the use of cloned animals can greatly decrease the number of animals used in experiments, because the effect of a drug can be tested on identical animals and no statistical normalisation requiring larger numbers of animals is required. Only by studying complex animal systems will the effects of altering genes be seen in transgenic animals, and be understood.

New strains of mice have been made as experimental models of human disease. Animal models (especially mice) have been bred for models of dwarfism, diabetes, sickle cell anaemia, muscular dystrophy and immunodeficiency diseases. Other animals have been made to study the effects of

different possible cancer-forming genes and genes involved in development. Drugs for use against AIDS are being tested in mice with a human immune system. The mice were developed with a deficiency called 'severe combined immune deficiency' and are abbreviated SCID-hu mice (the 'hu' stands for human tissue). 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 may be preferable. The mice strain used is genetically devoid of any immune defences so when human tissue (usually the thymus tissue which contains immune cells) is implanted mice respond as if they had a human immune system.

Genetically-engineered animals that are very sensitive to carcinogens, can be used as more sensitive 'probes' which is dramatically reducing the number of animals used. It is estimated that a carcinogen-sensitive mouse called 'Oncomouse' may lead to some tests for chemical carcinogenicity being compressed from three years to three months. There is also a microbial assay test, the Ames test, that is faster and more desirable than traditional animal testing. If this is realistic, net costs for experimental animals, as well as the total number of animals used in such studies, will drop dramatically.

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, lack of co-ordination, and susceptibility to stress. This emphasises the fact that there is a need for more basic research before undertaking gene transfer experiments. 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 illustrates 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.

The ethics of some of this work is challenging in the context of making very unusual and often diseased animals, although medical researchers justify this on the grounds of potential application of the research to untreatable human diseases. Genetic engineering has been used to make vaccines against animal pests, and to protect animals from disease. These could be argued to benefit the animals themselves, and so be on the positive side. 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. Conventional animal breeding dramatically illustrates the variety of dogs that we now accepted as commonplace. 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. However, there is a point beyond which it is unethical to use animals as a means to an end.

5.5.2   Ethical limits of animal use

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. This is a moral issue. There will be further refinement of regulations and development of ethics in the future, and it is possible that public acceptance of animal use in agriculture and research may change.

Government regulations on animal use and experimentation emphasise the importance placed on the avoidance of pain, and regulations limit the amount of animal suffering and experimentation. It will never be sufficient to justify animal use solely on the grounds of these experimental benefits. 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, create further potential for changing the physiology of animals, but there may be other uses of animals that are more unethical. The changed animals will be used to improve agricultural strains.

5.6 Medical ethics

There are many applications of genetic engineering to medicine, and some of these have been discussed in Chapter 2. The production of biochemicals, hormones, therapeutic proteins and vaccines using these techniques are the proven benefits of genetic engineering. There is nothing novel about the ethical problems in the use of these products in medical care, and they must proceed through the standard protocols for clinical approval. Their safety needs to be established, and they must provide medical treatment that fills a need.

5.6.1   Pre-natal genetic screening and selective abortion

Abortion is a contentious issue, as is human embryo research. They are separate issues to genetic engineering, but overlap in some applications. We refer readers to *Shaping genes* for a critique of these topics. New genetic techniques have made it possible to detect many genetic diseases, at increasingly earlier times during pregnancy, which is a medical advance that many women and families can take advantage of. It is important to note that after a positive diagnosis, and confirmation of the result (as mistakes occur), the mother may decide to have an abortion or, for some diseases, to commence medical therapy on the fetus. The technique of genetic screening is also recommended for people who do not agree with abortion, as it may be medically advantageous to know the genetic condition of the fetus before it is born, so that therapy, or extra educational, economic, social and emotional preparation for the birth of a child may be arranged.

5.6.2   Privacy of genetic information

Knowledge of the total human genome sequence raises many questions about the rights of individual privacy. This is a key issue for the future as it will be possible to screen for so many genes. The type of information produced ranges from a predisposition to diseases, or the certainty of knowing that a later acting disease will develop. 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 pre-natal screening and selective abortion or therapy. Decisions must be made about personal health risks that may be affected by diet, smoking, etc., and the type of work. The genetic information can be of great benefit to the individual person wanting to know about his or her genetic constitution.

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. Gene monitoring is targeted at a group, to determine whether a carcinogen is present in the workplace.

Screening for susceptibility to lung disease if an individual is exposed to asbestos might be an advantage if an alternative job in the company can be found. This has already been used to prevent people from working in some factories. It may become an excuse for companies not to hire susceptible workers, or women of child-bearing age, instead of cleaning up the factory. On the other hand, if a person suffers from haemophilia it would be wrong not to warn them of the risks of becoming a butcher. Decisions regarding insurance schemes and retirement are also involved. It is difficult to prevent insurance companies from genetically screening potential clients to reduce costs. Several recent studies of this issue have agreed that the only ethical, and most practical solution, is to provide nationalised health care, and social security. Society must make decisions as to whether it wishes to adopt this system.

If we consider individual human life to be of a high status then 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. This will mean sharing the cost of health insurance, and disability pensions, as in the past. This issue is very important, more important than some of the other issues that attract our attention away from new genetic technologies. The law must protect privacy of genetic information, as the alternative is widespread discrimination against many people. International law is required, as well as a change in society.

The call is for any employer or insurer not to discriminate. Government action to support prohibition of any form of discrimination, whether racial, sexual, religious or genetic, will be required. 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.

5.6.3 Gene therapy

The goal of biomedical research has always been to alleviate human suffering. The technique of gene therapy provides new approaches to achieving this goal. Just because a new technology becomes available it is not necessarily the most rational approach. Gene therapy has been described as a preventative therapy, preventing disease at the fundamental level. We should not forget that other causes of disease, and poor health, such as diet, and lack of health education, need 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 without the need for precise regulation of gene expression. What is essential is full public review of the results, which will have to be debated further before the techniques are more widely used. The results of gene therapy and comparisons with the 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 long term follow-up studies of patient progress.

The use of somatic cell gene therapy has been analysed very extensively by ethicists, medics, and numerous writers. In fact, if it is shown to be safe and effective, it may replace current unsatisfactory treatments. The first clinical trials are underway, and it should be judged in a similar way to other experimental medical treatments. Considering that the first approved experiments went through eight different committees for ethical approval, our response might be to say that it may in fact be over-regulated in the USA. When the procedure is safe and effective, it will become routine and will be introduced to New Zealand. It is very difficult to predict the time, as the technology is rapidly developing.

The extension of gene therapy to germline, or inheritable gene therapy, is now possible, but the ethical implications are still being debated. There are many ethical problems to be discussed, and they will require much more public debate before such techniques are ethically possible. In July 1990, a workshop/conference on human genetics and ethics organised by the United Nations CIOMS (Council of International Organisations of Medical Sciences) was held in Japan. Representatives from 30 countries, with expertise in science, law, ethics and public policy debated these issues. The conference called for extensive public discussion over this issue, and for the need for any national ethics committee that considers germline gene therapy to consider the international consequences of such therapy, because people travel between countries and it would affect the entire human race eventually.

5.6.4   Human genome project

There are major applications and implications of human gene mapping (refer Section 2.3.6). The human genome project will be a huge resource of information for medicine in the next century. There have been many potential ethical and legal problems raised, especially over the scale of the information. 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 GMOs and in turn expand conventional symptomatic therapy to many more diseases (supplemented by somatic cell gene therapy when appropriate). Mapping of the human genome will also expand our basic knowledge of human biology and consequently medical treatments. It is obvious that within the next few decades medicine will undergo a major change as the beneficial side of our newfound knowledge is harnessed. 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 30 years since we identified the mutation that causes sickle cell disease, but we are still developing effective therapies.

Genetic knowledge will allow ideas of eugenics to be explored. We need to maintain a distinction between diagnosis and treatment of disease, and selection for desirability. The ethical debate must focus on how to use the new information, rather than on whether to discover it. We must avoid stigmatisation or ostracism and labelling in general, and look at the individual psychological responses. Not only is discrimination a problem, but so is stigma. People can misinterpret information in idiosyncratic ways. Parents feel guilty about transmitting an 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 young adults may be encouraged to hide the information so that they do not become undesirable marriage proposals. There may be later guilt reactions and other psychological problems.

The ownership and control of genetic information and the consent to use such information must be addressed. More serious consideration must be given to personal reproductive decisions in the future, making life more complicated while hopefully improving its quality. We should note that the amount of information obtained will overwhelm existing genetics services, and geneticists. More training in genetics (as well as in ethics) will be required for physicians and health care workers. The time is right for much discussion about 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. It is important that widespread education takes place at levels understandable by the public. 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 of the information, we should not expect disease to be cured within 20 years. Genetic engineering will not be a panacea for the world's woes. New Zealand should expand the school syllabus to include coverage of recent genetic developments so that tomorrow's adults are prepared for these advances.

5.7 Protecting future generations

A common feature of issues raised by genetic engineering is that we need to consider the effects of technology on future generations to whom we have a responsibility. The beneficiaries and those at risk from the technology may not yet exist. The human genome project raises similar ethical and legal issues to those raised by current genetic screening, including confidentiality of the results. However, screening on a huge scale, for many disease traits and susceptibility to disease is inevitable. It is important that we deal satisfactorily with the test cases, before we are faced with this new information.

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 unenforceable. If another agent intervenes, or something unexpected happens, it is not considered our fault. Genetic engineering changes our moral horizon.

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 ethics are important for public policy decisions, beyond the physician's concerns with each patient, or the scientist's concerns with increasing yield of a crop.

Researchers may be held accountable for secondary consequences of their research. It may be very difficult to predict what will happen in the future. If social ideas change, then so may the pressures for genetic technology, such as the desire to use genetic enhancement. We need to ensure that future generations retain the same power over their destiny as we do, while benefiting from the culture and technology we have developed.

There is a growing realisation of the interdependency of the new genetic technology and the conservation of our genetic heritage in gene banks. The erosion of our genetic resource needs to be minimised because of its vital importance for the future development of industries based on plants and animals. The gene banks can also be improved through the use of new genetic techniques

for mapping genes, as well as the application of tissue culture techniques to vegatively propagated plants etc. Genetic resource conservation is both a global and a New Zealand economic issue. It has also become an ethical and cultural issue in recent years with increasing awareness of the importance of conservation and the long term sustainability of biological systems.

CHAPTER 6

Safety issues

"You can stop splitting the atom;
You can stop visiting the moon;
You can stop using aerosols;
You may even decide not to kill entire populations
by the use of a few bombs.
But you cannot recall a new form of life."
Edwin Chargaff, Science 1976

The fear of harm or unknown effects was cited as an objection by 40% when genetic engineering involved humans, 30% involved animals, 51% involved microbes and 39% of the people were opposed to plant genetic manipulation in the New Zealand survey. The fear of the lack of controls or possibilities of abuse of the techniques were expressed by about 10% of those opposed to each category of genetic manipulation. Thus, safety concerns are clearly an important issue.

During the past 15 years safety standards have been developed in genetic engineering laboratories based on the containment of GMOs. However, during the past decade there have been cases of deliberate free release of GMOs. People are concerned about unpredictable disruption to the ecosystem. This is complicated by the possible transfer of novel genes to other species, such as the 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 when the environment is harmed.

6.1 Risk, safety and the effects of uncertainty

The term safety is often found in the scientific literature in a context that suggests that a particular situation or activity is "safe". This is, in turn, interpreted by the lay public as implying some sort of absolute. When it is found that this is not the case, public trust in the scientific community is eroded.

Risks exist throughout our everyday life. The question of concern is not the existence of risk but the degree of risk. We may say that riding a bicycle is safe, however, in making this statement we do not take into account the car driver who turns without looking. In common with the scientific concept of safety we tend to ignore the effects of uncertainty.

If we think of risk as being a compound of the probability of an event occurring and the magnitude (in terms of potential damage or loss), then there are two uncertainties. In terms of a particular decision to release GMOs there may be uncertainty as to the possible outcomes of that decision as well as uncertainty as to the relative probabilities of the outcomes. People view risks in different ways and the factors that appear to have the greatest effect on people's attitudes towards risk are

the voluntariness of exposure, the perceived degree of control, and the nature of the possible consequences. From this perspective genetic engineering applications score negatively on all these counts.

Safety can be viewed in the context of "acceptable risk". There is a considerable body of literature that considers the question "how safe is safe enough?". What we are implicitly seeking is a general yardstick against which risks can be measured and judged "acceptable" or "safe enough". Because of the various factors associated with the way in which the public ascribes risk, as opposed to statistical calculations of risk that are specific only to particular circumstances, it is not possible to calculate such a yardstick and therefore risk assessment is used as a means of providing a surrogate measure.

Risk assessment comprises the technical evaluation of the probability of occurrence of all known outcomes as well as a social and political evaluation. A useful technique applied in risk assessment is the comparison of risks (costs) and benefits. This is a particularly appropriate mechanism to use for the determination of safety factors in genetic engineering. Safety, therefore, is a relative concept, and when scientists talk about safety it is important to remember that to maintain credibility with the public they must qualify the term "safe" so that members of the public can use their own judgement to determine the acceptability or otherwise of the hazard. Risk assessment cannot deal directly with uncertainty, which may involve a lack of knowledge about either the possible outcomes of their probabilities, but sensitivity analysis can assist.

6.2 Risks to whom and what

"Hazardousness" is another important concept related to risk. A hazard is the potential harm that may result from a risky decision. Where there is a perceived lack of control and voluntariness the public tends to view the possible detrimental consequences as having greater significance than the level of risk. This can be clearly seen with the nuclear power industry controversies. Similarly, the public tends to view the potential harm of genetic engineering much more seriously than the probability of that harm occurring.

The risks of genetic engineering need to be carefully examined and analysed for each application for release of a GMO. There is also a need for continual monitoring and evaluation of the safety standards in place and provision of swift action where necessary. One way of categorising the types of risks that may arise is according to the area where the costs fall. Risk assessment is a very appropriate technique for examining costs, risks and benefits. In general, however, it does not take proper account of equity issues.

Public concern focuses on whether the decisions made about the use of genetic engineering, which will involve the creation of altered or new life-forms, will be left to the discretion of individual scientists and corporations. Regulatory and advisory committees must have representatives of the public included so that they are seen to be neutral and balanced. Discussion over planned experiments should be carried out in the public domain, which will also aid the education of the public, if done in a reasonable way.

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 that they become trusted. Although it was scientists, and not the public who first flagged the issues in the early seventies they have missed many opportunities to tell the public what is going on.

Even the existence of good science journalism and television science programs can do little to dispel the public impressions created by a single popular movie or editorial cartoon. The 1987 OTA survey in the USA found that the public is more inclined to believe environmental groups than federal agencies or companies, and this trend was also detected in the New Zealand survey (Couchman and Fink-Jensen, 1990).

6.3   Case-by-case risk modelling

Because different organisms can behave in very different ways, and through genetic engineering pose different potential problems, it is generally considered preferable to use a case-by-case assessment. A systematic method of risk assessment must be used. Our understanding of the risks presented by genetic engineering is much greater than several years ago, but scientists cannot be complacent. There have been calls for a moratorium on the release of GMOs, but the only way to learn how to handle GMOs is to have controlled field trials.

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 the release of GMOs at an experimental level, risk assessment is needed. The first part of risk assessment is risk identification, after which comes risk estimation. 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.

The five main criteria for evaluating environmental impact include:

- 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.

In February 1991 the USDA published voluntary guidelines for consideration by researchers when releasing GMOs. The guidelines divided into classes and gave directions on how to conduct trials safely. At the beginning of May 1991 the USDA had issued or was considering 173 permits for the release of GMOs. Experience gained from implementing and monitoring trials is proving data that will be used to develop better regulations.

A procedure called GENHAZ for estimating the risks posed by each organism has been developed by the Royal Commission on Environmental Pollution. GENHAZ is a procedure enabling scientists to undertake their own environmental assessment of each new GMO for potential release. The idea is similar in principle to the USDA voluntary guidelines but has advantages for New Zealand in that scientists are largely responsible for their own safety procedures: a situation ideally suited to

GENHAZ monitoring. These two procedures are useful models for New Zealand and are based on recommendations from researchers and provide alternatives to case-by-case risk modelling.

Although rules will impede some research, there is reason to be cautious. The British Royal Commission pointed out that the biggest brake on the accelerating number of releases would be a case of serious damage caused by slack regulations. Closer examination of each case would consequently be justified. It also recommends that carefully monitored environmental releases will make a greater contribution to safety than a moratorium. A problem with this approach is that we may not know which experiments are particularly hazardous or their risks until the experiment has been attempted.

6.4 Risks from research or industrial applications

In the 1970s scientists imposed voluntary guidelines effecting a moratorium on several types of genetic experiment involving the use and construction of genes and their insertion into vectors for their multiplication in bacteria. This moratorium has lapsed now that the potential hazards have been assessed; it was decided that suitable physical and biological containment should be adequate.

"Biological" containment advocated the use of "crippled" host cells and vectors. These host cells and viruses 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 practice 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 as strict as biological containment, but is still maintained for work on tumour or disease-promoting agents. Before the appearance of GMOs harmful effects resulted from the accidental release of micro-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 this experience is a powerful example of the risks of accidental release of new organisms.

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. The current concerns include:

- 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 micro-organisms not known to acquire them naturally.

The principal problem now in all work is not mechanical, but is one of laboratory discipline. Safety committees exist in all major laboratories, but there is still room for laxity. Medical surveillance of laboratory workers should be more common in case there are any long term effects. Commercial scale release involves bigger growth chambers, or land area, and increased wastes, but there is now 10 years of experience using GMOs in fermentations, and the technology is constantly improving.

6.5 Release of genetically-modified organisms into the environment

To be of major practical use to worldwide agriculture, any GMO must be released into the environment. There have been about 400 known experimental field releases of GMOs (not including the different sites used for the same GMOs in each country), and about 16 (Section 3.6) in New Zealand. The deliberate environmental introduction of any new organism, including GMOs, should only be 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, that need to be maintained.

Activists opposed to genetic manipulation 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 and there have been a number of major reports on the release question. Serious ecological concerns are raised, and ecologists stress that the organisms 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.

The first experiments are being conducted in as closed environmental situations as possible. The initial experiments on plants and animals are in enclosed research areas, but when they have proved safe and are economically useful, they will need to be grown in large quantities. It may be feasible to use enclosed farms for some animals, especially fish or chicken, or even pigs or cattle.

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 were introduced to solve one problem but caused another. Some previous releases of organisms into new environments have proved to be beneficial, or at least harmless, but others have been deleterious. In the case of New Zealand, some imported organisms, such as clover, trout, sheep and pine trees, have resulted in agricultural and recreational benefits. In other cases imported organisms have had detrimental impacts on the environment in terms of economy, loss of native species, health problems and effects on cultural values.

6.5.1 Examples of field trials of genetically-modified organisms
While there are relatively few examples of the release of GMOs into the environment, there is considerable information on the dispersal of bacteria. 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.

One famous test case in the United States concerned the field-testing of a recombinant strain of *Pseudomonas syringae*. 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. A strain of *P. syringae* was constructed that was incapable of initiating ice formation until the temperature dropped to about -5°C. The modified bacteria were sprayed onto plants displacing the unmodified bacteria of the same species. Field trials were performed to test whether the non-nucleating strain (Ice-) would 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 potentially this bio-control system could reduce 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 was the possibility of accidental release of the organisms by the protestors and vandals who attacked the research sites. Both strawberry and potato plants were involved, and there have been many independent field experiments to evaluate the dispersal, effectiveness, environmental fate and competitiveness of the bacteria as well as its chance of spreading into the ecosystem. Previous laboratory studies suggest that there would be an extremely small likelihood of these strains surviving outside the area of use. The observed environmental behaviour showed little spread and a relatively short life.

There have been several trials involving recombinant vaccines. Rabies is important in Europe, where about 1.3 million foxes are killed annually in attempts to control the disease, and there are one to four human deaths. Recently, recombinant vaccinia virus vaccine has been introduced in Belgium and part of France in bait to protect foxes against rabies. Rabies viruses have also been field tested in the USA, and some have been approved for field release.

A recombinant Hepatitis B vaccine has been approved for use on human beings in most countries in the last five years. Research is underway to develop vaccines for Hepatitis A, dengue haemorrhagic fever, leprosy, leishmaniasis and respiratory syncytial virus, to name a few. Recombinant virus-based vaccines offer some advantages for controlling disease because they can express the antigenic determinants for more than one infectious agent, and thence reduce the costs of administering the vaccines. 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.

An unauthorised test of a vaccine was performed in an attempt to vaccinate Elm trees against Dutch Elm disease. It was conducted at Montana State University by the researcher, 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 non-recombinant, 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. The primary danger was the deliberate release of Dutch Elm disease, a very harmful disease, rather than the novel bacteria. This illustrates the very real danger that it is easy to ignore the rules.

The International Commission of Epizootics plans to immunise hundreds of millions of cattle with recombinant vaccinia virus expressing rinderpest antigens because 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.

Attenuated strains of *Salmonella typhimurium* as vaccines have been tested in Australia. Salmonella is important in the sheep, cattle and poultry industries and is also a human health risk. The vaccine was pre-release tested in sheep in pens by the CSIRO. It proved effective in these trials. A test is currently underway involving fewer than 100 sheep, and the project is expanding.

In Britain there have been several field trials of GMOs. One series has involved baculovirus insecticides - viruses that only infect and kill a few species of insect. The viruses 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. The objective of genetic modification is to improve their speed of action because they normally take several days to have an effect. Insertion of toxin genes into the virus spreads the action of the bacilloviruses. The results of the experiments indicate no enduring and unpredictable side effects.

The world's first commercial pesticide based on a live genetically-engineered organism went on sale in Australia in March 1989. It is called No Gall, and it protects stone fruits, nuts and roses from Crown Gall disease, which causes worldwide annual losses of at least US$150 million. The "pesticide" consists of a harmless strain of the disease-causing bacteria that will live on the same leaves as, and produces an antibiotic that kills, the disease-causing strain. The gene for this antibiotic is on a plasmid that has been engineered to prevent its transfer to disease-causing bacteria. Resistance to the antibiotic is thus prevented. An 18-month trial prior to commercial release was undertaken. There are still some opponents to the release of this bacteria in Australia and there have been calls 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.

Initially trials of genetically-modified plants can occur in closed greenhouses, however many plants respond differently to conditions in a greenhouse compared with those in the field. 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. Field trials have been set up involving genetically-modified alfalfa, rape, tomato, Oilseed rape, poplar, potato, sugarbeet and tobacco. A variety of herbicide-tolerant genes have been tested in different plants. There have also been trials involving inserted *Bacillus thurengiensis* insecticidal protein genes in potato, tobacco, and tomato. Increasing numbers of trials are underway in the USA.

Only limited trials of transgenic farm animals have been undertaken so far because no useful traits have consistently been expressed. Small, closed experimental farm trials have been underway for several years in Australia and the UK. Larger trials are expected soon and will challenge regulators.

6.5.2 Persistence of genetically-modified organisms

Since most GMOs only differ from the parent strain in one or a few genes, they will often behave in a similar way. Yet many GMOs will probably be less fit than the parent organism. However, if this is the case it may take many generations before the introduced organism disappears due to decreased fitness if the turnover rate of population is slow. A variety of responses are 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 artificially-bred crops such as potatoes can become a weed in ensuing crops.

Natural selection acts on all organisms, including GMOs. Selection after the release of the GMO may reduce costs associated with novel traits.

Released micro-organisms are highly likely to enter freshwater or marine environments via agricultural run-off or faecal contamination. Various environmental factors affect persistence, including moisture, pH, temperature, nutrient level, sunlight and other organisms e.g. predators. Introduced strains of *Rhizobium* inoculants may not compete successfully for nodule formation with indigenous populations of *Rhizobium*.

In some cases, the GMOs may be intended to persist at a particular level in the environment. If the GMO is intended to enter a new ecological niche it may be safe. Those organisms used for biocontrol may be required 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, such as micro-organisms that break down particular toxic waste in emergencies. GMOs should be designed for safety in addition to their function. This may mean that the GMOs feature 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.

Detection and subsequent elimination of organisms may be feasible if they are large, such as large animals or plants. However, insects, micro-organisms or viruses may be difficult to exterminate after introduction. All detection methods used have limits, and it may not be possible to ensure that a micro-organism is eliminated. The absence of an immediate negative effect does not ensure that the effect will never occur, it may take time.

6.5.3 Transfer of genes

The fact that interspecific gene exchange occurs naturally may also provide an argument that the spread of engineered genes to members of the natural community must be anticipated. If lateral gene transfer occurs, an engineered gene may persist in the natural environment after the GMO is eradicated. An important unknown question is how often lateral gene transfer occurs. Scientific evidence suggests that among micro-organisms it is neither sufficiently rare that we can ignore its occurrence nor sufficiently common that we can assume that barriers crossed by modern biotechnology are comparable to those constantly crossed in nature.

Microbes

If we generate novel genetic combinations it is important that experimental observation of organism behaviour takes place. One possibility is that bacterial viruses could acquire a capacity to infect higher organisms, which may upset the extremely intricate ecological balance. The genetic barriers thought to exist between species are in fact often broken. For decades plant breeders have used comparatively crude techniques 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. It is unlikely that there will be problems with single, precisely engineered gene alterations unless one of the gene vector's attributes is to move to other organisms under field conditions.

Several systems have been devised for tracing the fate of genes in genetically-modified bacteria in the environment. The first spray releases of genetically-engineered ice nucleation 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 of the cells were directly deposited onto the plants and soil. Of the bacteria that entered the aerosol spray, eight percent drifted out of the plot into buffer zones. The maximum drift was between 20 and 35 m away. On subsequent days, depending on the wind movement, some re-suspension from plant and soil surfaces occurred. Computer models have been developed on the basis of the results from field trials to aid assessment of future trials.

Several types of barriers exist to reduce the transfer and stability of genetic information introduced into an ecosystem. Environmental barriers include the avoidance of contact. The success of these barriers depends on the concentration of the gene transfer system in the ecosystem. Particulate matter may have a significant effect. There are different ways of stabilising recombinant plasmids. Disabled plasmids that are not capable of gene transfer at a level that is detectable can also be made. It is also possible to use self-destructive GMOs, as previously described.

Plants

If the trait that is being transferred to a plant is already expressed in the environment then there is generally less concern about its transfer, especially if the particular engineered gene is present in the system within which the trial is conducted. To avoid the selection of new genes it has been suggested that genes should not be linked to antibiotic-resistance genes because these are steadily being selected for by the extensive use of antibiotics. Kanamycin-resistance markers are commonly used in the laboratory selection of transgenic plants, but, kanamycin, the antibiotic, is only used in the laboratory. The chances of the gene in the plant being transferred to bacteria is extremely low, and has yet to be demonstrated. However, even if the transfer from plant to bacteria were to occur at a frequency of one 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 one is already resistant to kanamycin.

Crop plants vary greatly in their potential for hybridisation. At one extreme there exists crops that 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 that originated by hybridisation. It is undesirable for crops to transfer some genes to their wild relatives because the wild relatives could become competitive weeds.

Experiments should be done to determine the distance over which pollen spreads (on insect vectors this can be over large distances), and how it results in hybridisation. Plants often show little barriers to hybridisation, so there is always a potential for exotic pollination. 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.

A British programme called PROSAMO (Planned release of selected and modified organisms) has been underway for three years and involves trials of GMOs at different sites to test their survival and effect on the environment. The programme is 50% funded by private companies, who hope that the safety results will be positive and will speed up the introduction of larger scale releases of GMOs. The first report produced under this programme found that GMO plants appear not to be invasive or persistent in field trials.

A recent study has been carried out at DSIR Crop Research Division, Lincoln, to examine the extent of pollen dispersal. 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 one percent, but only five in 10,000 of the progeny from wild-type potatoes planted up to 4.5 m from the trial were transgenic. Continuing experiments are producing more impressive results and substantially less pollen dispersal. There have been no transgenic progeny recovered from wild-type potatoes growing 4.5 to 10 m from the trial.

This type of study is very useful for risk assessment, although in some 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 but many of the new traits will be beneficial to weeds, such as pest resistance.

6.5.4 Potential ecological effects
The most likely potential ecological effect of the release of GMOs will be protection of the environment from many harmful chemical pollutants. If plants used fertiliser more efficiently, less fertiliser would run off into rivers and cause pollution, and if plants were pest and disease resistant then fewer problems would arise from the poisoning of the environment by fungicides.

Most planned introductions of GMOs are likely to be agricultural in nature. The negative consequences will probably also be in the agricultural area. If the introduction is 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 release of a GMO has an impact on the natural community, the consequence would probably be restricted to a transitory disturbance of the community structure.

From past mistakes we should recognise 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 one percent have become pests. Biological 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.

In New Zealand, 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. Thus, with careful evaluation and pre-release 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. New pests could arise, for instance a salt-tolerant rice cultivar may escape from cultivated fields to estuaries. It is possible for both native or exotic species with new traits to become pests. Sometimes a change in the environment can render a plant a major weed. Release of a genetically-modified cultivar in regions where that cultivar has many wild relatives could result in hybridisation between the cultivar and its wild relatives. Enhancement of the effects of existing pests could occur if they hybridise with GMOs. Weeds could acquire herbicide resistance, or insect resistance, or other traits advantageous to them.

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 functions are genetically performed by a range of organisms in microbial communities, in many cases there would be little concern over microbial species replacement by an introduced GMO. 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.

There are several models for ecological relationships but all have limits. The overall record of few hazards stemming from the release of products of traditional agricultural breeding does not necessarily mean it is safe to proceed with release of GMOs. Although negative effects have not been seen from the experience with GMOs accidentally released from laboratories, it does not mean that this is a justification for the release of GMOs.

6.5.5 Factors important in applications to release genetically-modified organisms
In conclusion there are several major sequential steps that should be followed when generating GMOs for release 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.

International agreement must be reached on the information to be provided for regulatory consideration. The key elements that need to be considered include:

- identity of personnel involved (qualifications etc.)
- objectives of release
- location of proposed release, geographic and environmental information
- descriptions of parent organism, vector, GMO
- description of the manipulations used to produce the GMO
- arrangements for release, preparations, timing, method, decontamination

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- potential environmental effects
- monitoring arrangements
- contingency plans in case of unexpected events
- results of prior local consultation and assessment.

6.6 Food safety

At recent conferences on GMOs concern has switched from the environmental issues to concerns about the safety of the end product for human consumption. Two recent reports (IFBC 1990, WHO 1991) provide an in-depth analysis of the scientific basis for concerns about the safety of food derived from genetically-engineered organisms and suggest guidelines for the assessment of potential hazards.

The level of public concern in New Zealand was measured in the recent survey and is illustrated in Figure 6.1.

Incidence of concern about using various
products produced with/from GMOs
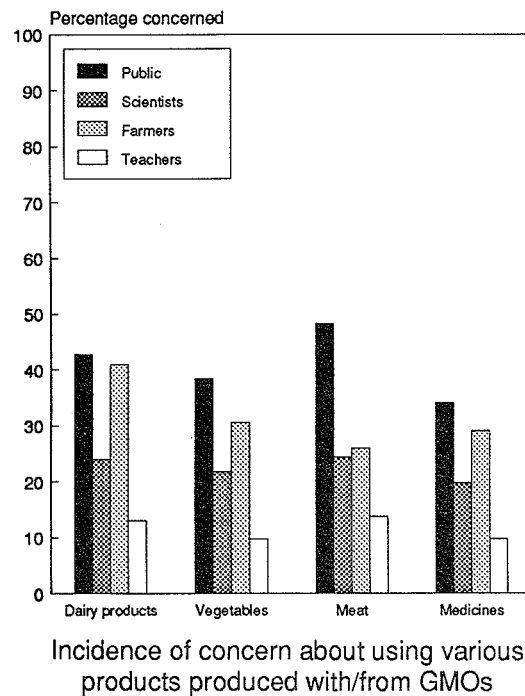
Scientists and teachers are more aware than the public and farmers that GMOs can be used to produce food and medicines. Three-quarters of the public (75%) and of the farmers (76%) were aware of the fact, compared with nearly all scientists (95%) and teachers (97%). In no case were more than half those surveyed concerned about eating products of genetic engineering. Among the public, eating meat derived from genetic engineering technology causes most concern (48%), followed by dairy products (48%), vegetables (38%), and medicines (34%). Among farmers, dairy products cause most concern (41%), followed by vegetables (31%), medicines (29%) and meat (26%). Scientists and teachers are much less concerned about eating such products and no category causes much more concern than any other.

Possible unknown effects or side effects as a result of ingesting such foods are the main concerns among scientists and teachers. The public and farmers that felt uneasy thought such foods were

"unnatural" and could have unknown side effects. They express more general food safety concerns. In the case of medicines, the predominant concern of farmers was the possible lack of information and the potential for unknown effects or side effects.

6.6.1 Novel foodstuffs

A wide range of novel foodstuffs is beginning to appear on the market. The British Government recently approved the production of a genetically-manipulated strain of bakers' yeast. Maltose permease and maltase genes from the yeast were combined with new promoters from another strain of the same species. The yeast takes up and digests 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, BioTechnica, 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. This allows faster brewing, and the beer requires no additives to remove starch. The unpasteurised beer, when sold and consumed, would still contain live yeast.

It is expected that approval for human consumption of a genetically-engineered tomato produced by ICI in Britain and Calgene in the USA, will be given in the next year or two. This tomato has an antisense gene that inhibits the production of an enzyme which causes the softening of fruit after ripening. Plants that are genetically modified may require some preliminary testing to ensure that no secondary toxic product has been produced after the manipulation.

The bacteria that are responsible for tooth decay are being genetically manipulated in the USA so that they do not produce tooth-decaying acids. The new strain could be applied in toothpaste, or it could be applied once for life if competitive with other mouth bacteria. This may pose interesting regulatory problems, as it will involve the continual exposure of users to the bacteria.

Recently, transgenic apple trees were made that were chimeric. Only the roots were genetically modified, the fruit-producing branches and fruit were not, therefore they would not be considered a genetically-modified foodstuff.

6.6.2 International guidelines

The long and impressive record of traditional plant and animal breeding in the pursuit of safely introducing new genetic combinations of crop food sources for human and animal consumption must serve as a basis for evaluating the safety of transgenic plants. Most of the perceived hazards relating to the safety of transgenic food products will only occur at very low frequencies, and would not pose any new risks over those expected from traditional breeding. In fact, the precise manner in which genetic engineering can control the nature and expression of transferred DNA offers greater confidence for producing the desired outcome than traditional genetics and breeding. Nevertheless, to ensure public acceptance of the technology, regulatory agencies should proceed with caution until more experience with foods derived from GMOs is acquired. Food should also be analysed for changes in the levels of significant nutritional components and natural toxicants found in the crop species and its close relatives. Appropriate animal tests should only be necessary when molecular, biological and chemical data do not provide sufficient assurance of safety. Doubt has been raised

over the need for current animal testing protocols. Any new paradigm established for assessing the safety of food resulting from transgenic organisms should also apply to products resulting from other forms of genetic manipulation, including traditional breeding.

In 1988, the International Food Biotechnology Council (IFBC) was formed with the aim of identifying the food safety issues and assembling a set of scientific criteria to evaluate the safety of food derived from plants and micro-organisms resulting from the applications of biotechnology. The Council discusses the variable composition inherent in foods and food ingredients, such as the nutrients and toxicants. There are several vitamins (A and 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. The Council 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. It was recommended that food from GMOs be regulated by existing law. This is also the recommendation of the Victorian Law Reform Commission. The possibilities of financial liability and legal suits in the USA will make companies very cautious. If the purpose of engineering is to introduce 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 genetically modified.

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

- uncharacterised genetic material presently consumed in food
- fully characterised genetic material derived from nontoxic, nonpathogenic micro-organisms 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: very 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.

6.6.3 Public acceptance

It is important to confirm that genetically-modified products are not only harmless to animals but are harmless to human consumers. 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%) by improving feed-conversion efficiency without any apparent change 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. 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, but they are still considering whether it is harmful to cows and should decide in 1991.

Many small farmers and the European 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 can get cheaper veterinary help. Even if BST is safe, consumer objection to milk produced using BST may be considered enough to warrant a ban in Europe. In early 1991 the Committee for Veterinary Medicinal Products of the European Community recommended the use of BST in Europe, but there is to be a moratorium on release until the end if the year. Its use is banned in the Netherlands, Denmark, Sweden and Norway.

In the USA there is also consumer rejection of BST-produced milk, and requirements that milk be labelled if BST is used. It should certainly be necessary to label products made using BST-treated animals; the public can then be involved in decisions about its use. Pressure from consumers has resulted in bans on BST-produced milk in some US states (Wisconsin and Minnesota), bans on the sale of milk products from BST-treated cows in six major supermarket chains, and a tape-recorded telephone hotline at the Consumer's Association. More than milk is at stake. What is at issue is the way that decisions on future agriculture are made. Even if BST has no effect on humans, it may still be banned for its mildly detrimental affects on animal health or for more politically important socio-economic reasons.

Consumer objection has delayed the introduction of the technology of food irradiation. Irradiated food has been tested widely and found to be safe if radiation levels are controlled. 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 a growing number of developed countries in addition to developing countries. It will only be used for up to five percent of the food in Europe.

6.6.4 Better products

Preparations of bacterially-produced "human" insulin have been available since the early 1980s. They were assumed to be better than porcine insulin, and most diabetics in Britain have switched to the human insulin. However, there are serious doubts as to whether it is actually any better. The reason for the widespread switching included 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, although some diabetics are allergic to porcine insulin.

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 US 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. Streptokinase is derived from streptococcal bacteria and commands a two-thirds share of the market for these agents in the USA.

Protein pharmaceuticals produced by recombinant DNA technology require approval. Part of this process involves the purity analysis of the product. In 1990 in the USA impurities in a vitamin supplement tryptophan made in a particular batch by a single producer have been found to be the cause of a disease called Eosininophilia-myalagia syndrome which caused several deaths. This has served as a warning that purification procedures should not be shortcut. 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. They can have immunological and/or biological effects. 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 along with new purification methods have produced the highest purity proteins that have ever been available for human therapeutic applications. 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.

The quality of genetically-modified products is regulated according to their intended use, not their method of manufacture. Existing laws ensure the safety and quality of these products. The list is expanding. According to the 1990 annual survey by the US 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 undergone clinical trials, and 14 more are in the final stages of trials on humans.

CHAPTER 7

Commercialisation and patenting life

"Pasteur was patenting yeasts in the 19th century, I can't see that simply because something is alive it should not be patentable." Tim Roberts, 1991

"In one regulatory stroke, the Patent Office reduced the entire animal kingdom to the lowly status of a commercial commodity, indistinguishable from electric toasters and automobiles." Jeremy Rikfin, 1988

7.1 Commercialisation and biotechnology

Genetic engineering has great economic potential. The total value of world sales of products derived from genetic engineering in 1989 was estimated to be US$1 billion, and by the year 1993 the value should be over US$3 billion. This compares to a total annual pharmaceutical market of US$1000 billion. The world market for seeds and agrochemicals is about US$70 billion. In the first half of 1991 the biotechnology business grew at a very fast rate, if the investment of money in stocks, is an indicator. In the first five months of 1991, 20 companies had gathered US$915 million in investments in the US stock market. Part of the confidence for this investment is thought to be the recent patent court cases that have indicated how the courts will respect patent rights for biotechnology that produces new therapeutic proteins as well as new production techniques. The two issues of commercialisation and intellectual property protection are inseparable.

In New Zealand there has been little commercial development to date but the potential is considerable. The commercial incentive for researchers to obtain intellectual property rights such as patents is strong and already licences for New Zealand genetic-engineering patents have been exported. In many cases patenting is the way in which basic research is channelled to commercial organisations. This type of technology transfer has aided the establishment of new ventures resulting in more research, more benefits from foreign currency earnings, access to new products, and the generation of employment for highly skilled people.

Many companies in the USA are, however, in financial difficulty because of factors including the long time lag between investment in research and returns from the investment. They may also be constrained by public fears and the complexity of regulations and patenting. It takes time to apply for the approval of environmental release for GMOs, and a long time in some countries to review it (in the USA it may take five to six months). In addition, there are long delays for consideration of intellectual property rights. There are about 7,000 biotechnology patent applications awaiting approval in the USA, and although it may take five to six years to clear the backlog, patent protection begins from the date of application.

There are also dangers of privatisation because of this long development phase. Recently, a major Italian biotechnology research centre that had been sold by the government was forced to close because the new company decided it was not profitable. It was one of the top government research centres when it was transferred to private control a few years ago; now the 80 scientists have been

made redundant. However, in the USA there are still venture capitalists who are investing in new biotechnology companies, with long term goals. Areas of investment include the design of novel drugs and hormones that go beyond the use of naturally occurring genes.

7.2 Public opinion about patenting life

Patents for individual molecules are held by different genetic engineering companies in a way 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 clean-up products. The first modern patent obtained for a living organism was obtained for a bacterium genetically engineered to digest oil slicks, after the court case Diamond v. Chakrabarty in 1980 in the USA. Patents can generally be sought either on products or processes used to manufacture the product. There are still differences between the systems used in Europe, USA, Japan and New Zealand, as well as other countries, however, a diplomatic conference was held in June 1991 seeking to harmonise subject matter eligible for patent protection.

The patenting of living organisms is a sensitive public issue in New Zealand and overseas, particularly when applied to animals. The New Zealand public opinion survey found that there is less public support for animal patents and for genetic material extracted from plants and animals than for plant patents (Table 7.1).

Some people find intellectual property rights on living things to be totally unacceptable (e.g. on moral grounds) while others are concerned about the social implications. Given that genetic material is now also patentable, the issue is of particular interest to those engaged in or funding genetic engineering research.

The New Zealand survey (Couchman and Fink-Jensen 1990) is the only one the authors are aware of, that has sought public opinion on this issue. People were first asked: "Have you heard of patents or copyright?" Those who had heard of patents or copyright were then asked: "In your opinion, for which of the following should people be able to obtain patents and copyright?"

Ninety percent of the respondents indicated that they had heard of patents or copyright, 10% said they had not. The table below shows the proportions of the respondents who had heard of patents/copyright and who agreed that patents or copyright should be obtainable for a range of organisms.

Table 7.1 New Zealander's approval of "patenting".

Area	Percentage approving "patenting"			
	Public	Farmers	Scientists	Biology teachers
New inventions such as new consumer products	93	94	95	88
Books and other information	85	82	81	72
New plant varieties	71	82	66	49
New animal breeds	59	68	63	49
Genetic material extracted from plants and animals	51	64	53	34

Table 7.1 shows that patenting of new inventions and information was acceptable to most people, while a large proportions did not agree that patents should be obtained for genetic material. While farmers obviously have a more "commercial approach" to patenting, biology teachers clearly have different views (12% did not approve of any form of patent or copyright).

The acceptability of patenting the different life forms varied significantly among the groups within the sample. Acceptance of the patenting of new plant varieties, new animal breeds and genetic material was generally higher among those aged 35 - 55 years and among those who were extremely interested in S & T (80%). When relating acceptance of the patenting of genetic material to the perceptions of genetic engineering that had been obtained earlier in the questionnaire, acceptability was found to be:

- lowest among those who had said they had not heard of genetic engineering (only 45% of whom said patenting genetic material was acceptable)
- highest among those who thought genetic engineering was a worthwhile area for research in New Zealand (59%)
- lower among those who said they had worries about genetic engineering (37% of whom said "no" to patenting genetic material) compared to those who did not (30%).

The patenting of life forms and genetic material is clearly a contentious issue for some individuals and groups in New Zealand, particularly among biology teachers. However, there appears to be a majority view that most forms of intellectual property rights for animals, plants and genetic material is acceptable to the majority of New Zealanders. It is clear from a moral and ethical viewpoint, that there is more concern where animals and genetic material are involved - a trend suggesting less support for patenting human tissue.

7.3 Patenting life

The major debate in Europe over the question of patenting life has been between the biotechnology industry with an eye to reaping rewards for their research investment, and groups of environmental, farming, legal and religious organisations who oppose patenting of genetically-engineered plants and animals. The difficulties may become even more vexing as the question of patenting sections of the human genome emerges. Many useful human and animal DNA sequences will have industrial applications in the manufacture of therapeutic proteins or DNA probes to detect genetic disorders. Patenting of animals and plants is possible in New Zealand (see Section 7.6) although human gene therapy may not be patentable under current law.

The current European controversy was fuelled by the recent case of a patent being granted for all non-human animals genetically modified with an activated oncogene, based upon a transformed mouse, later called "Oncomouse". The onco gene makes these animals more suitable for research in testing for sensitivity to carcinogens. Du Pont, the licensee of the Harvard University patent, is selling the mice at US$50 each.

Harvard University obtained a USA patent and then applied for a European Patent but was initially turned down. According to European Patent Convention Article 53(b), micro-organisms (this includes manipulated plants and animals) are patentable, but "plant or animal varieties or essentially biological processes for the production of plants and animals" are expressly barred. However,

Harvard has appealed this decision and a draft directive that all genetically-engineered plants and animals should be patentable is about to come before the European Parliament. 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. At least 10 countries permit animal patents, including New Zealand and Australia, and another 53 have not prohibited the granting of animal patents.

The New Zealand survey indicates that these issues are less contentious in New Zealand possibly because of our agricultural background, fewer environmental fears such as those held by people in West Germany and because of a better public knowledge about the environment in New Zealand. There is probably a greater acceptance that there is little ethical difference between a property right on an animal such as a racehorse or other types of improved new livestock, and alternative forms of personal property rights such as patents. After 150 years of animal breeding there may be some contentious issues, however, it is clear that animals may be patented in New Zealand - a process that appears to receive broad public support.

The major arguments for patenting animals in New Zealand include:

- patent law encourages inventiveness
- patenting provides an opportunity for reward for successful inventions
- other countries support patents, as should New Zealand if the biotechnology industry is to compete
- if patenting is not permitted useful information will become trade secrets.

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
- patenting may promote environmentally unsound policies
- patenting produces cost burdens on agriculture.

Most of the arguments against animal patenting will not be affected by permitting patents, as the issues are similar to those existing prior to the patenting debate (such as animal rights, adverse effects of high technology on agriculture, the distribution of wealth, international competitiveness). The different policy on patenting around the world reflects the level of controversy that this issue generates.

The most serious issues to emerge from this debate that have relevance to New Zealand are:

1. the broad nature of a gene patent that could be used for a wide range of purposes in many species of plants or animals

2. the difficulty of drawing a line between patenting human genetic material and human beings

3. the fact that farmers have the right to breed from plants or animals under plant variety rights-type protection, but not those under patent protection.

Answers to the problems are yet to be found. Some have suggested that alternatives to patents should be sought for genetically-engineered life forms. Alternatives might include plant and animal breeders' rights, registered trademarks or even direct subsidies or tax incentives for the industry from governments. The latter have been noted as generally less desirable than other alternatives to patents.

Animal variety rights that are similar to plant variety rights have been implemented in Czechoslovakia, Hungary and France, Germany and other European countries are seriously looking at this issue. Under this system, patents would be obtainable for processes that meet the patenting criteria, but plant and animal variety rights would be available for the final commercial product. Under variety rights, the holder must make the organisms available to all who request them at reasonable cost, thus protecting the inventor's investment, but only if they allow fair access to the organism.

New Zealand is currently reviewing laws governing intellectual property protection. Because of the importance of international trade in agricultural products and the current GATT trade negotiations on these issues, New Zealand must be seen to provide fair and equal access to intellectual property rights for residents and non-residents. New Zealand also has the potential to assist in the debate by having a well developed legal framework for patenting in this area and a clearer understanding of public opinion on the issue of patenting the results of genetic engineering than many other countries.

7.4 The legal position in New Zealand

There are three main types of intellectual property rights relevant to living matter in New Zealand. These are patents for invention governed by the Patents Act 1953, plant variety rights governed by the Plant Variety Rights Act 1987, and trade secrets which are governed by common law.

7.4.1 Patents

A patent gives the patentee the right to exclude others from making, using, selling or "exercising" the patented invention for a term of 16 years. It is a form of social contract between the patentee and the state. In return for the power to exclude others from using the patented invention, the patentee must make information about the invention available to the public. Where the invention involves the use of the inventive technique such as living matter which is not otherwise available, then the patentee must insure that the living matter is available through, for example, culture deposits in a recognised culture collection.

Patent validity requires three concurrent components: novelty, non-obviousness and utility. Obviousness is not considered during examination by the Patent Office and may be challenged, as it often is, before being granted. Utility is only considered in High Court proceedings, if revocation is pleaded by another party.

The expression "manner of new manufacture" has been developed to mean that there must be sufficient human intervention to distinguish the invention from living matter that is found in nature so that it may be industrially applied. To give an example, a bacterium was found in the sewers of Naples that produced, as a metabolite, a valuable antibiotic. Finding the bacterium in its natural

environment in the sewer was a mere discovery not amounting to an invention. However, when water from the sewer was screened and the bacterium isolated and put in a environment in which it reproduced itself and concurrently produced the antibiotic, it become an invention.

In New Zealand there has not been any controversy in either the Patent Office or the courts over the "patentability" of living matter. The only controversy involved a determination of what constituted sufficient human intervention. Recently changed policy within the Patent Office now states that provided living matter is defined so as to exclude the state in which it occurs naturally, then it is eligible for patent protection. An example of such a definition would be: "*Streptomyces aureofaciens* in a biologically pure form" compared with its natural state.

A 1983 decision of the New Zealand Court of Appeal held that a method of medical treatment of humans is not patentable subject matter but material for treatment is patentable. Thus, patents for products are more sought because they have more value than patents for processes. This ruling may mean that gene therapy may need to be considered from the commercial product angle as opposed to 'use'. The exclusion of medical methods of human treatment from patenting does not extend to the treatment of animals, which is patentable subject matter.

An invention is novel if it has not been published or used commercially in New Zealand. The pre-existence of an invention is not a novelty bar. In a decision of the New Zealand Court of Appeal involving a synthetic antibiotic, ammoxycillin, the Court held that there could be a patent for an isolated epimer that had the totally unexpected property of absorption in the blood stream, even though there was a prior patent for a racemic mixture including that epimer. This example raises the question of whether use of the racemic mixture would be an infringement, since the benefits of the 'good' epimer would still be present and available.

Whether or not an invention is inventive is determined by an objective test on a subjective basis. The invention must not have been obvious to a person of average skill in the art. Obviousness is judged at the time the invention is made, not with the benefit of hindsight.

7.4.2 Plant variety rights

A plant variety right is the right to exclude others from producing for sale or selling reproductive material of the protected variety. In New Zealand the right also extends to the propagating of protected varieties for the purpose of commercial production of a product. A typical example of the latter activity is the grafting of apple tree budwood onto rootstock for the purpose of the commercial production of apples.

There are two main exceptions to the plant variety right. The farmer's privilege allows a farmer to collect seed of a protected variety and to plant that seed for the farmer's own growing purposes, but not for the purpose of producing seed for sale. The breeder's exemption allows a plant breeder to use material from a protected variety to produce a new variety. Sale of that new variety is not an infringement of the plant variety right for the variety from which the new variety was derived. After three years from the date of being granted, reproductive material of the protected variety of reasonable quality must be reasonably available at a reasonable price or third parties may apply for compulsory licences to sell plant material of that variety.

To be eligible for a plant variety grant, a new variety must be distinct from all other varieties of common knowledge. Reproductive material of the variety must not have been sold for more than one year in New Zealand (four or six years outside New Zealand, depending on the type of plant) before making an application. Populations of the variety must be homogeneous within the limits common to that species. Varieties must be stable from generation to generation.

7.4.3 Trade secrets

A trade secret is information or living genetic material itself that is of commercial value. To qualify as a trade secret the owner must have gone to reasonable effort to protect the nature of the information or material. There is no absolute property right in a trade secret to prevent anyone else from making commercial use of the information. The owner of a trade secret only has the right to prevent someone, who has improperly taken that trade secret, from taking commercial advantage of the information. The owner of a trade secret cannot stop somebody who has independently developed the information themselves. Perhaps the most famous example of a trade secret is the recipe for Coca-Cola.

It has been held in an Australian court that a piece of nectarine budwood incorporating the unique genetic information of that variety is a trade secret. The theft and subsequent grafting of that budwood without the permission of the owner was a misuse of confidential information. The person who grafted the budwood was liable in damages to the owner of the budwood.

Maintaining living material as a trade secret is an alternative to patenting. It is possible to seek protection through a trade secret provided that the material itself can be maintained in a secure facility and its identity cannot be determined by "reverse engineering". If someone independently and legitimately obtains the living matter, the owner of the trade secret cannot prevent exploitation by that competitor.

7.4.4 Inter-relationships

The three different types of intellectual property rights - patents, plant variety rights and trade secrets - can partially or completely overlap or can be mutually exclusive. Trade secrets and plant variety rights are mutually exclusive. Once a plant variety right application has been lodged then it is open to public inspection and its subject is no longer a secret.

In New Zealand a pending patent application is not published until after it has been accepted by the Patent Office. An applicant for a patent can abandon the application up to its acceptance date and treat the invention as a trade secret. However, once an application has been published the information in that application can no longer be a trade secret.

The rights under a patent and a plant variety right grant can be complementary and in some instances can be in direct conflict. For example, if a gene causing expression of a fungus-repelling metabolite that causes harm to tomatoes were found in another plant and transferred to the tomato plant, several types of intellectual property rights could be granted. A patent could be granted for the following different aspects of the invention:

- the DNA sequence comprising the gene
- the transforming vehicle, such as a vector or plasmid

- the process of transformation
- the tomato or any other plants transformed.

The patentee will probably have described the transformation of at least a single variety of tomato, thus creating a new, distinct variety. That new variety of tomato, assuming that it satisfies the other eligibility criteria, will then be eligible for plant variety rights protection.

Someone producing for sale or selling reproductive material of the new tomato variety would be infringing both the patent and the plant variety right. If a transformation had been done by a person other than the patentee, then there would be conflicting rights. The owner of the plant variety grant would not be able to produce and sell the protected variety without infringing the patent. The patentee would not be able to sell reproductive material of the protected variety without infringing the plant variety rights of the grant owner. That conflict would have to be resolved by a commercial settlement involving a cross licensing arrangement. There are compulsory licensing provisions under both the Patents Act and the Plant Variety Rights Act that either party might try to invoke if there were a complete stalemate.

7.4.5 Enforcement

The enforcement of patent or plant variety rights in living matter has not been considered by the courts in New Zealand. It is not possible to state with certainty how far the patent will extend. If one purchases a patented product such as, for example, a garlic crusher, one does so with an implied licence to use it as one sees fit. However, animals and plants reproduce themselves. The purchaser of a patented animal or a plant may have an implied licence to use that animal or plant for all purposes without fear of infringement. If one of those purposes is to reproduce in the form of other animals or plants, it is open to question whether the next generation of animals or plants are merely the result of an implied licensed use of the invention or whether their production and existence constitutes an infringement of the patent.

This very issue was considered in the diplomatic conference in March of 1991 by the 20 countries that make up the International Convention governing plant breeding rights (UPOV). It was agreed that the production of a new generation of plants infringed the plant variety right in the parent variety.

7.5 Agriculture and society

There is a movement in society to re-focus attention on less economically-oriented goals. As groups such as the Green Party in Europe become increasingly powerful politically, these goals will be realised. There is also a philosophical movement against the rapidity and extent of change in society. This view is stronger against corporations that are seen to be making money without considering social and human factors. One issue that has been highlighted is the generation of herbicide-resistant plants by companies that have commercial interests in the herbicide sales. The commercial strategy for chemical companies is to gain increasing market share through a shift in the type of herbicide use, not to increase overall use. However, there has been an adverse reaction by some groups who argue that multinational chemical companies plan to increase herbicide use and farmer dependence on seeds that require herbicide use. A balancing factor, however, is that the availability of patent protection for living matter is an incentive for chemical companies to conduct

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research into biological controls of pests and diseases to meet popular demand for less use of harmful chemicals.

Increased yields of agricultural products will mean that farmer subsidies for excess production may need to be changed. The average annual yield increase is one to two percent, however biotechnology may allow greater increases. The present production levels have led to a variety of "food mountains" or "milk lakes". These problems will be further exacerbated and the area of land required to grow some crops will substantially decrease. This in itself may be environmentally advantageous, but it will change the structure of farming. We can only hope that benefits of increased agricultural productivity are shared by developing countries who, because of their high population growth, have greater capacity to absorb increases in food supply. The economic system in these countries will thus be challenged and much more than agricultural policy will consequently be affected.

Criticism has been made of the use of bovine somatotropin (BST); although it increases milk production in cows, it may have negative effects on farmers. It may leave the 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 representing only one interest. Industrialised countries in Europe and America and Japan protect small farmers to avoid social costs. In USA, the state of Wisconsin has banned the use of BST for this reason.

New crops might also accentuate inequalities in the farming population. Farmers may become more dependent on transnational agribusinesses. Small farmers can compete 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 who prefers milk produced on farms that do not use BST. It is however, potentially dangerous to leave society's fate up to market forces.

Subsidies for farmers in New Zealand have recently decreased. They may consequently be in a better position to adapt to change than farmers overseas who continue to receive high levels of subsidy. It is estimated that each European family contributes over $20,000 annually in farm subsidies.

7.6 Developing world interests

Poorer nations tend to oppose intellectual property rights that may monopolise control over areas such as food and drugs that are vital to economic growth. Industrial countries, particularly the US, argue for the same protection in the developing world as elsewhere. This argument was pressed in the recent GATT negotiations.

Lesser (1991), in his review of patenting and PVR in lesser developed countries, suggests that rather than having a negative effect, patents promote domestic inventive activity. He also concludes that the existence of patents does not generally and necessarily lead to monopoly or dominance by larger firms. If, through lack of patent protection, developing countries delay their access to new technology, development may be impeded.

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Biotechnology undoubtedly has the potential to aid developing countries through universal vaccination programmes, new crops etc., but there are also concerns about access to and payment for germplasm and the potential of biotechnology to produce industrial substitutes for traditional crops.

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. Thomas Jefferson said "the greatest service which can be rendered to any country is to add a useful plant to its culture". The introduction of kiwifruit to New Zealand is one such example. The raw resources of the new biotechnology industry are genes. Many of the useful genes exist in a wild state in countries of the developing world. The poorer nations claim that patents on improved crops devalue the vast genetic diversity, the value of which is enhanced by the new techniques of genetic engineering. If the developed nations "help themselves" to this diversity, it is regarded as a threat to the countries from which the genes are obtained. The issue is however a complex one as the third world has the genetic resources needed to increase food supply and security, while the rich world has the know-how and capital to use them. Gene banks and germ plasm stores (mostly under the control of developed countries) are seen as an important medium for preserving and ensuring free access to germplasm for food crops. Government support for these gene banks and international collaboration in preservation and exchange is a critical issue. However, in spite of the effort invested in gene banks, diversity is still declining rapidly and urgent international action is needed to halt the decline.

Several positive initiatives are developing that indicate a willingness of developed countries to help lesser developed countries:

- The World Intellectual Property Organisation (WIPO) has developed a model industrial property law (recently revised by W. Lesser 1991) to meet the differing needs of developing countries. WIPO and UNESCO have also approved a model law protecting communities' rights to folklore - it allows societies to have clear title to their genetic resources.

- At least one major biotechnology company has offered all the genetic material it isolates for free use by the International Rice Research Institute and related Centres for International Agricultural Research (CGIAR). Negotiations continue with other companies to make similar gestures.

- FAO is working towards the establishment of "Farmers Rights", a levy on new genetically-engineered products that could provide for a balance between the rights of the "formal innovators" and the "informal innovators" - the farmers, their countries and communities who have developed and conserved the genetic diversity on which the innovations are built. Although several key countries have been reluctant to support an FAO-based fund, recent progress by a group of seed companies and government scientists is likely to result in an independently-managed fund used for genetic resource conservation and utilisation programmes with an emphasis on *in-situ* conservation.

CHAPTER 8

Policy issues and recommendations

"The complex evolution of biotechnology as a policy issue can be summarized by an analogy using the genetically engineered Harvard Mouse. In the 1960s the question of the mouse would have centered on whether in theory such an accomplishment in genetic engineering could and ought to be done. In the late 1970s the question would have focused on the implications if the mouse escaped from the laboratory. In the 1980s the question of who owns the patent on the mouse takes center stage. In the 1990s it is likely that the focus of debate will be on who will build the better one and where." L. Christopher Plein, 1990

8.1 Introduction

The purpose of this publication is to discuss the issues associated with genetic engineering. The issues fall into two categories: ethical issues and safety issues. Solutions to problems raised by ethical and safety issues revolve around the way in which we conduct our research and the care with which we introduce new products to the market and/or the environment. In approaching these issues fundamental questions are raised: Regulation or voluntary compliance? If we choose regulation, can the law protect an ethical viewpoint? If we choose voluntary compliance, will the public good be protected? A second purpose of this publication is thus to suggest possible solutions to the problems raised by these issues.

As a nation we need to be aware:

- of the growing public awareness of the potential benefits of genetic engineering and the concerns about its application
- of the rapid progress of commercial applications for the technology
- that research is resulting in a sharp increase in the number of GMOs being introduced into the environment
- of the fact that at present there is no enforceable control over private sector activities
- of the perceived potential for danger.

8.1.1 Regulation or voluntary compliance?
Decisions need to be made about the need for regulation at a number of levels:

- genetic manipulation research involving serious animal, plant or human pathogens
- large scale experiments involving GMOs
- introduction of GMOs into the environment
- commercial products of genetic engineering (developed in New Zealand or overseas).

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The potential advantages of a regulated environment include:

- that something is seen to be done to effect control
- maximum control should ensure maximum safety
- applicants are aware in advance of the requirements
- cases are open to public scrutiny
- direct comparisons between similar applications may be made.

The potential disadvantages of regulation include:

- procedures that may be inflexible
- the need for regulations to be enforceable
- the possible need for various levels of regulation for various levels of risk, scale and type of activity
- its potential to be bureaucratic, expensive and anti-competitive
- its potential to cause delay with consequent reduced benefits
- inhibiting the introduction of non-target organisms i.e. regulation may influence control of conventional plant and animal breeding.

There are a number of dilemmas that face regulators:

- the organisms that are to be included must be carefully defined, taking into account the fact that the definition of a GMO may be ambiguous
- there must be consistent regulation in the context of different levels of regulation (local, regional, national)
- the regulations should be statutory, with little room for challenge by petty court cases
- the regulations need to apply to all research - private and public
- consistent penalties for violators must be assigned
- public opinion in the local area, as well as over the whole country, must be considered
- for regulation to be effective it must be enforceable.

If the premise is adopted that a national regulatory agency is required to act as the public's agent, then there are a number of management options and tools that are available to such a regulatory agency. These include:

- the use of a checklist approach for the evaluation of proposals
- some form of generalised control, where basic principles and objectives are defined by the agency and administered by groups undertaking activities
- a requirement for formalised risk assessment
- the use of codes of practice
- industry-defined voluntary measures
- use of expert referees.

These options and tools represent varying gradations on the theme of regulation. In practice, an agency may choose to use all six options or combinations of them for different aspects of its operation.

8.1.2 Can the law protect an ethical stance?

Ethics are about the rightness or wrongness of human conduct. The law, however, is concerned with the public good. There are many ethical views about the degree of human intervention in the genetics of other species that is acceptable, and the uses to which genetic engineering should be put.

If, as a nation, we attempt to compromise incompatible ethical positions there will be many critics. While the law should be consistent with the ethical views of the majority of people, the key issues are where the law should intervene to control a process, when it should make an activity criminal, and whether such law is enforceable.

8.1.3 What role has education?

Public awareness of genetic engineering is high but the depth of knowledge is low. "The new genetics" will have a considerable impact on the economy and the lives of New Zealanders. Education therefore has a key role to play in enabling citizens to understand genetic engineering, to use the technology effectively and to enable public debate of the related bioethical concerns. The education issue has already been identified in Europe as a barrier to pubic debate and regulatory understanding and is being addressed by the industry and the European Commission. A number of important education issues require attention:

- It is important that education in genetic techniques and genetic engineering is introduced at a lower level in schools and that suitable mechanisms are found for new developments to be quickly incorporated into the school syllabus.

- Existing tertiary science courses must be updated more rapidly and students taking related courses in commerce, law, engineering and social sciences should be made aware of the impact of the new genetic technology.

- There is an urgent need for members of the public to be informed about techniques, issues and alternatives so that they can be fully involved in the debate on and decisions made about these issues. Some work in this area has already been funded by DSIR, however, this funding has been discontinued under the premise that public education about science is the role of the Ministry of Research, Science and Technology.

- Health care workers need some basic training in genetics and genetic counselling. Members of the public must know some basics before they can be informed consumers and users of these services. They also need to be exposed to the language of probability and risk.

8.2 Research

8.2.1 How do we encourage research?

The extent to which commercial biotechnology should be encouraged in New Zealand must be addressed. There are difficulties in securing private funding of long term research as well as a lack of both venture capital for and knowledge about this technology at board level in New Zealand companies. Government will consequently need to consider its approach to industry support if it is to foster private innovation. The governments of many countries are investing money to aid the commercialisation of biotechnology despite policies discouraging the use of public funds for private business. In March 1991 the Australian Government paid A\$7.3 million to keep Sirius Biotechnology in the business of fermentation-based biotechnology and the US government has been investing much larger sums in similar ventures.

A key issue in encouraging investment in biotechnology research and development is the need for legal protection for the products of that research. The costs of innovation persist in the long term and are thus expensive, while imitation costs are low; patent protection can be a key incentive. Most nations are now considering the forms of intellectual property protection that are desirable for products of biotechnology. Decisions must be made about those products and processes that should be patentable and how far patent claims should go. Several aspects of patent law require review:

- The law regarding what is found in nature and what is regarded as having sufficient human intervention to warrant patent protection needs clarification.

- The issue of whether patent claims on animals should extend to progeny, is rather uncertain and would depend on the invention and the way the patent claim is worded. Breeding or reproducing a patented organism could amount to copying the invention and would not be permitted without the permission of the patent holder. Plant variety rights have solved this problem by allowing the "farmers privilege" although this is currently being reviewed nationally and internationally. Some organisms e.g. yeasts, cannot be limited practicably. However, in other cases, such as farm animals and commercial plant cultivars, multiplication would need to be restricted in order to obtain a profitable return for innovation. The issue needs clarification in the current review of intellectual property law.

The current status of patent law is confusing in the area of broad claims for compounds or genes that may be produced in different ways or inserted into a range of organisms. The cost of permitting such monopolistic patent claims seems more than is necessary to encourage innovation.

Patents are specific to the nation that issues them, however, most countries protect against foreign production by barring the importation of a product if producing it locally would have infringed a local patent. However, while it is clear that direct products of patented processes cannot be imported, the question of importing more indirect products, which may arise from GMOs or the progeny of a patented organism, has yet to be clarified.

8.2.2 Should research be nationally planned or co-ordinated?

Intelligent and rational use of New Zealand's limited resources for genetic engineering research requires a clarification of research goals. Although research in New Zealand is generally planned from the grass roots up, some national planning and co-ordination may also help to allay public concerns about the wise use of publicly-funded research.

It is likely that New Zealand can obtain a competitive advantage in certain areas of genetic engineering research in both the public and private sector. **The government should encourage researchers to set up an advisory body together with other appropriate people to act in an advisory capacity and to undertake some strategic planning for this area of research.** The Advisory Committee on Novel Genetic Techniques (see Section 8.2.4) may be an appropriate body to undertake this role. One of the major functions of such a body would be to set national biotechnology goals and research priorities. The setting of these priorities would require consideration of possible future markets and co-ordination with other related research in agriculture, social, environmental, education and health areas.

Advice on funding research in genetic engineering should naturally follow such strategic analysis. It is likely that such advice would be welcomed by the Foundation for Research Science and Technology, and would also encourage collaborative research between public and private sector organisations.

8.2.3 Should certain areas of research be restricted?

There is increasing international acceptance that the process of genetic engineering in the laboratory should be pursued, subject to containment procedures, without any general limits. There are two exceptions.

■ *Pathogenic organisms*
There are two major concerns raised in the area of pathogenic organisms. The first is the development of offensive biological weapons. Although genetic engineering research could be clearly used for such research objectives, the abhorrence of such technological developments would prevent any rational scientist or research institute from participating in such research. If a terrorist group wished to pursue such developments it would be performed secretly without any concern for ethics or containment, no matter how restrictive or severe the research guidelines or penalties are made.

The second concern involving research in pathogenic organisms is the inadvertent production of an organism with greater pathogenicity or host range. However, such concerns should only relate to the release of GMOs from the laboratory, and not to laboratory experimentation, provided experiments are performed under appropriately contained procedures. Genetic engineering research on pathogens can provide a valuable research tool for understanding the basic biology of these organisms. Such research results can lead to the design and development of resistance mechanisms to pathogens and/or the production of vaccines.

- *Animal research*

The growing international concern for ethical animal treatment has resulted in an evaluation of research procedures and establishment of ethical committees to monitor research on animals. The humane treatment of animals requires that when satisfactory alternative experimental approaches, such as cell culture techniques, can provide the same or similar conclusions, then animal experimentation should not proceed.

There are already appropriate controls on animal research in New Zealand with all projects being reviewed by local ethical committees. However, the necessity of such research needs to be continually monitored. There are some animals used in medical research in New Zealand that have been genetically modified to provide appropriate research models. As long as the animals are not suffering, and society decides that limited use of animal research is permitted, then there is no reason to regulate such research further.

Government regulations that require animal testing of new drugs and compounds need to be continually reassessed in the light of the development of alternative testing procedures. Animal experimentation is often undertaken because regulations require humans to be protected from the unforeseen effects of drugs or new medical therapy. The new genetic techniques and embryo manipulation will substantially reduce the number of animals used in vivisection.

In Britain, transgenic animals can now only be researched under licence from the Health and Safety Executive. The Committee of that Executive recommended that the licence should cover the breeding of transgenic animals until it can be demonstrated that the progeny are not likely to suffer adverse affects. 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 restriction applies to the creation of new breeds made by genetic engineering techniques.

8.2.4 Are our research guidelines up-to-date?

In 1978 the Advisory Committee on Novel Genetic Techniques (ACNGT) was established to oversee guidelines for laboratory containment of recombinant DNA research. Any public institute involved in this area of research must appoint a Supervisory Committee and a Biological Safety Officer who have the responsibility for enforcing the recommendations made by ACNGT. However, this requirement does not extend to private organisations.

Current ACNGT guidelines were last revised in 1982 and are now outdated. They establish five levels of containment (CO to CIV) and provide guidance notes for the categorisation of each type of experiment. In view of the international experience with contained use of GMOs, and the experience in developing new regulations, such as the GENHAZ procedure recommended in Europe, the New Zealand regulations should be updated and simplified. GENHAZ is a form of voluntary risk assessment undertaken by researchers that can assist in streamlining applications for release.

8.3 Regulation

There are several options when regulating the release of genetic engineering and the release of GMOs. These include:

- detailed legislation, which would need constant revision as new technologies emerge
- establishment of a central Statutory Committee, with flexibility of control to adjust to new situations
- a Central Advisory Committee with codes of conduct for voluntary compliance
- Regional authority control, perhaps with advice from a central advisory committee
- no control, perhaps with certain high-risk exceptions.

International experience with these options would suggest that the establishment of a central Statutory Committee, with flexibility of control, would be the most appropriate option for New Zealand. This Committee would ensure that a responsible approach was seen to be taken to safeguarding the community and the environment (see other reasons Section 8.1.1).

8.3.1 A central regulatory committee or regional control?

The lesson to be learned by New Zealand from other countries is to decide on sound national legislation and to settle for only one layer of regulation. Regulation in New Zealand may be affected by the Resource Management Bill which has an emphasis on control by regional authorities. However, central decisions are felt to be more appropriate for New Zealand because of its small size and:

- the potential spread of GMOs between regions
- the need to avoid any region becoming a testing ground for poorly designed field releases
- the lack of scientific expertise in the disciplines of molecular biology, ecology,and other relevant areas such as risk assessment within a region preventing the formation of more than one expert committee
- the need for links with national bioethics and research planning organisations
- additional costs associated with several regional authorities compared to one central committee
- the potential for provinces and Maori tribal regions to intend to regulate overlapping territories and to make conflicting decisions
- the need to avoid bureaucratic hurdles that may discourage research in some areas.

Possible mechanisms enabling local authorities to comment on specific regional interests could be built into any central control system.

Ecological effects and geographic ranges of organisms transcend political boundaries. It is therefore essential that international co-ordination of risk assessment and regulation be promoted. The OECD is reformulating guidelines, which may be harmonised with EEC guidelines. The ultimate aim is to harmonise worldwide regulations.

8.3.2 Is it the product or the process that is important?

In the USA the Environmental Protection Agency and the USDA no longer discriminate between new organisms that may be genetically modified, but focus on the **properties** of the organism. This approach is increasingly being accepted by other countries facing regulatory control.

In 1989, the US National Academy of Science published a report that stressed two themes. Firstly, that there is no conceptual difference between altering an organism using classical breeding approaches and gene splicing; and secondly, that 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 approach is endorsed by the Ecological Society of America, but the Society also notes 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. **One approach may be to review all new organisms, giving more attention to those made using genetic engineering, an approach endorsed by the Ecological Society of America.** If such an all-encompassing approach was adopted then exemptions should also be stated.

Some countries are already making specific exemptions from review, these include:

- Large scale fermentation procedures using genetically-modified bacteria, provided GMO bacteria have been found to be safe under past experimental experience.
- GMO organisms that are functionally identical to organisms that could be produced using other methods that are not now subject to review (although possibly there should be some review of these organisms).
- Techniques that involve only naturally occurring processes of reproduction including selective breeding techniques and *in-vitro* fertilisation. This exemption covers the release of organisms made by any naturally occurring process, modifying 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.
- As most new vaccines for serious diseases are produced using recombinant DNA techniques, there should be little need to review each case.
- Organisms involving gene deletions and gene rearrangements within a given species of microorganism (because these alterations can all occur naturally).

8.3.3 Need for public participation?

There is clear public concern about those decisions on the use of genetic engineering to alter or produce new life-forms that will be left to the discretion of individual scientists and corporations. Does the public have a say in how this technology is used? Are cultural sensitivities considered? Are safety issues thoroughly investigated? Are ethical issues considered?

Clearly if the public is involved as members of regulatory committees and by public announcements of intended releases of GMOs, there will be more confidence in the regulatory processes. Maori people must also be represented in the decision-making process because of their particular interests, and the responsibility of the Crown to consult over resource use and management issues.

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While some information may need to be restricted for reasons of commercial confidentiality and to prevent field trials from being disturbed, all information should be provided to the committee, in confidence. Those parts that the committee agrees are commercially sensitive, and unimportant for public comment, could be withheld from public exposure and comment.

There is a need for a national bioethics committee that would be similar in nature to the medical ethics committee and would have an advisory role similar to that of such committees in other countries. In the USA, the slowness of government to face controversial issues such as human genetics and reproduction has led to non-government organisations establishing national bioethics committees. New Zealand should establish a committee that is accountable to the public.

8.3.4 How should genetically-modified organism releases be handled?

At the time of going to press a new policy has been drafted by the USA White House Council on Competitiveness suggesting that GMOs "shall not be subject to federal oversight" unless there is substantial evidence that they present "unreasonable" risks. Previous regulations have been criticised by the Council as "regulations that discourage or penalise innovation". While there has been widespread condemnation of this approach by environmentalists and industry, New Zealand must be mindful of the need to strike a balance between reasonable control for safety purposes without the need for over-regulation.

An independent statutory committee is needed to consider applications for the release of new and GMOs in New Zealand. This committee should be separate from the research advisory body but should have established links with it. As there is a limited amount of expertise available, this committee would build on the work of the IAG and should be established centrally, but it could be extended by the use of regional and local representation. The public should have access to this committee through submissions and hearings.

Controls for both laboratory experiments and release applications should be established as soon as possible. Policy makers must determine whether the most appropriate way of approaching control is through the setting of guidelines and voluntary compliance, or by regulation. In either case, a monitoring system should be established to govern both public and private sector research and applications.

Various criteria can be used to determine whether an application is inherently safe. These include whether:

- the GMO duplicates the phenotype and community relationships of naturally-occurring organisms
- the GMO will survive or reproduce after release
- the genetic material can be transferred to other organisms by known naturally-occurring processes
- the functions of the gene will have adverse effects on the environment
- the genetic material is derived from pathogens and known to be responsible for the pathogenic nature of the donor organism
- there is past experience with a similar organism or GMO.

A 1989 report by the Victoria Law Reform Commission in Australia recommended that specific legislation be drafted in the area of regulating GMO releases. 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, for an environmental assessment to be conducted prior to release, for public advertisements and information concerning the release to be made available for comment, and for releases to be subject to approval from the appropriate government agencies.

8.3.5 Should industrial production of genetically-modified organisms be regulated?

Industrial size presents problems of a larger scale. Precautions such as the sterilisation of waste products is costly, but adequate disposal procedures are required for all applications and experiments.

Safety assessment must take account of the characteristics of parental and modified organisms, health considerations such as pathogenicity, and environmental considerations. There should be methods for decontamination of areas in the event of accidental releases. Various classes of operation must be provided depending on the organism. While research up to a certain scale may be exempt from regulation, industrial-size proposals should be submitted to a regulatory committee.

It is especially important to include private companies in the scope of these regulatory guidelines and to make guidelines statutory. Given the small size of the New Zealand research community, researchers in the private and public sectors should be encouraged to utilise the specialist advice that a committee will be able to provide. Suggested guidelines follow those of the European Parliament (Table 4-1 in Macer, 1990).

8.3.6 Should there be controls on medical genetic information?

Our knowledge of genetics is increasing at a tremendous rate. New genetic knowledge will result in cheaper, faster and more accurate genetic tests. However, society is not yet equipped to receive this information. **Decisions must be made about what information to communicate to people, to whom it should be communicated, when and how. Research must be undertaken on the implications of passing on this knowledge at different stages of life to people with genetic disease.**

The establishment of government genetic registrars may be beneficial to the provision of health genes and to genetic research, providing that there is sufficient protection to prevent problems arising from possible abuse, breaches, of confidentiality etc.

It is important to protect confidential data about individuals from several groups including employers and medical insurance companies. Yet without systematic genetic screening of applicants for medical insurance, screening is effectively carried out by asking questions about family genetic disease.

8.3.7 *Should the safety of the product be controlled?*

In many European countries, novel food proteins are not subject to special legislative approval. Food additives, however, are required to undergo safety appraisal. The term novel food protein can include sources of protein not previously exploited for human consumption, including novel enzymes from GMOs. Regulatory control of new genetically-modified foods needs to be considered.

No particular harm is introduced into a food because it has been produced by a plant or animal variety that has been genetically modified. **However, existing standards for food safety require independent review from specialists in food science, health, and genetics. Food product labelling** may be necessary to aid and protect consumer choice.

8.4 Some important consequences

8.4.1 *Do our genetic resources need protection?*

The value of a nation's genetic resources is increased by the new genetic technology. The decline of wild genetic resources is also occurring at an alarming rate both in New Zealand and overseas. **Thus, there is an urgent need to ensure that New Zealand's genetic resources are adequately protected.**

- New Zealand currently has no legal protection against other nations or organisations exploiting our genetic resources without recompense. Thus, it is in New Zealand's interest to support international moves to provide protection through patent law (see Section 7.6). New Zealand should also support efforts in international fora, such as GATT and the forthcoming UNCED conference, to recognise and financially acknowledge countries (particularly developing countries) that are sources of genetic material subsequently used by technology-rich developed countries.

- New Zealand currently provides minimal support for international agencies such as those within the Consultative Group on International Agricultural Research (CGIAR) network that work to preserve, create and use genetic resources efficiently. Full membership and participation in CGIAR should be an urgent priority for New Zealand both in terms of our international responsibilities to 'pay' for the benefits we already receive, and as part of our role as a nation with a huge stake in international trade.

- These factors serve to emphasise the need for a comprehensive review by the Ministry for the Environment into New Zealand's needs and responsibilities for the protection of its native and adventive genetic resources. Such a review is required to examine the appropriateness of current genetic conservation in the light of the new legal and technical issues that genetic engineering presents. This review should be undertaken in consultation with a broad range of community and research groups.

8.4.2 Who will be financially responsible for releases that go wrong?

There is considerable uncertainty over the actual risks of ecological or crop damage from deliberate release of GMOs. Many risks may be characterised as low probability but high consequence type. There will be various types of risk to health, food safety, ecosystem disruption, pollution and technology failure.

One way to put a cost on the risks is via insurance brokers. **Those releasing transgenic organisms may have to accept product liability and insure themselves.** Lloyds of London view deliberate release as an insurable proposition. The risk assessment procedures will require expert advice, but this has been done in other cases of technological risks. However, we should not leave it to the market to decide upon the costs of a release that "goes wrong". The costs of an accident are unknown.

It is difficult to assess all the benefits that flow from the introduction of new organisms, although many direct benefits can be identified. It is also difficult to value parts of the environment in a monetary way. It may be considered appropriate for the approved and small-scale field testing of GMOs to be protected from financial suits, but for commercial-scale releases to be insured. The responsibility for any problem that eventuates may need to be assigned to either the approving committee or the manufacturer; it seems appropriate to assign immunity to the farmers using new organisms.

CHAPTER 9

Conclusion

A wide variety of genuinely important concerns have been expressed over genetic engineering. They fall into two classes: those that depend on personal opinions, and those that depend on science (such as risk assessment). Both are important in the future development of genetic engineering and the setting of limits to its application. Society needs to decide which experiments and techniques it is willing to support given the wide range of implications of genetic engineering. If New Zealand can improve public understanding of genetic engineering there will be a better climate for innovation in knowledge and access to genetic resources. The two factors will give New Zealand a competitive advantage and enable investment to be targeted at key technological developments.

In agriculture there are definite advantages in some artificial reproduction, embryo transfer, clonal reproduction, and genetic engineering. This does not raise significant ethical dilemmas if there is no harm done to the animals. Transgenic animals raise two major issues: environmental release and ecological dangers; and vivisection issues, such as animals that are susceptible to disease or are regarded as 'unnatural'. Although the New Zealand public is aware that the benefits of genetic engineering generally outweigh the risks, they are more concerned about the genetic manipulation of animals than they are about the manipulation of plants and microbes.

The main concern about transgenic plants and micro-organisms is the question of environmental release, and safety of foodstuffs. The key principles involved are stewardship of the earth and safety. While the many advantages of this new technology are obvious we need to be careful that it does not result in the wide distribution of detrimental genes in the ecosystem. An over-regulated approach to controlling the technology may result in missed opportunities. For New Zealand this would mean a loss of economic and environmental benefits arising from the reduced use of agrochemicals and the substitution of biodegradable products for older toxic products.

Other concerns raised by genetic engineering techniques, such as commercialisation and sustainable agriculture, are more complex issues. Questions about how we should apply these techniques, who should use them, whether they should expect profits from them, and political implications are more difficult to assess. 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. The technology may have greater implications, in terms of social change, than the risk of ecological harm associated with GMO release.

The decisions about genetic engineering must take into account many considerations, extending well beyond the scientific merit or the opportunities suggested by its application. These decisions are often difficult or controversial and good public relations are important. Independent regulatory control is likely to be needed to monitor procedures used in risk evaluation and safety.

Much research is underway in New Zealand that uses biotechnology. Given the suitability of New Zealand for utilising new developments in agriculture there is still a huge potential for more research. Worldwide there will be less demand for basic staple foodstuffs as agricultural productivity

increases. Genetic engineering will undoubtably assist in the development of novel quality products. New Zealand economic interests may also be well served by investing in the production of high value products, such as pharmaceutical and human medical proteins, or food products, using plants and animals. The returns on a single protein can be of the order of several hundred million dollars annually but after long term research and development and safety testing of the product. This commitment is possible, however, with long term research funding.

Policy makers need to consider international work because considerable research has been conducted into developing safety regulations. The special concerns of New Zealanders also need to be respected. Some questions, such as the safety of GMOs for industrial use or free release, and food safety, are primarily scientific questions. The decisions about 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 also be more subject to public opinion.

This publication is presented to stimulate discussion on the issues associated with genetic engineering, to suggest possible approaches to these issues, and to provide a target for criticism. It has made some suggestions for broad policy development. Options such as the establishment of a single regulatory committee for the regulation of genetic engineering reaffirm the *status quo* but research guidelines do require revision. However, issues such as patenting of animals, medical implications, and the issue of bioethical controls require a greater level of in-depth research and consultation than the constraints of this study permit. Ideally, working groups should be set up to discuss these ideas in consultation with the community.

Acknowledgements

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Further reading

Several books are recommended for those seeking more scientific background and insight into ethical and regulatory issues. These also provide extensive bibliographies for those who wish to study these topics further.

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