Journal and Proceedings of The Royal Society of New South Wales

Volume 118 Parts 3 and 4 [*Issued March, 1986*]

pp.157-164 Return to CONTENTS

Genetic Engineering - By Man For Man

W.J. Peacock, FRS, FAA

[Address to the Faculty of Science Centenary Celebrations at the University of Sydney on 14 May, 1985.]

In the past few years biologists have learned to cut and join DNA in a controlled manner. DNA is the molecule which codes our genetic makeup. It contains the blueprint for our development. Each cell in our body contains 46 chromosomes and each chromosome is one long DNA molecule with genetic message enough for 1,000 genes. The gene is the unit of the genetic language – a language of 3 letter words and a 4 letter alphabet.

We can now isolate a gene, study it, change it, and in some organisms reinsert it into the chromosome so that it functions properly again. Also we can join a gene from a human or a wheat plant into the chromosome of a bacterium or vice versa.

This recombinant DNA technology is the basis of genetic engineering – the controlled manipulation of the genetic constitution of a living organism. Such manipulation almost always involves one or more processes carried out in a test tube in a laboratory.

Genetic engineering has revolutionised biological research. This is certainly the age of biology, not of computer science or atomic physics. Genetic engineering has also revolutionised the public's perceptions of biological research. It is an emotional subject. Often the emotions are fear and worry, this, frequently, because of misconceptions and misinformation.

Genetic engineering, or molecular biology in a broader sense, is my science, and I'd like to share some of that science with you tonight and I hope appraise you fairly of what it is and what problems there are in the way in which it interacts with us and our society.

Genetic engineering will soon impinge in many ways on our daily lives. A family at breakfast may eat a breakfast cereal which has an advertisement on the packet stating that the cornflakes are amino acid enriched – this having been achieved by genetic engineering to adjust the proteins in the seed of the corn crop. They may then have some bacon which may have come from a pig production system where the rate and extent of growth of the pigs had been enhanced by the provision of pig growth hormone; which had been produced in a bacterial culture fermentation system, the bacteria having received a pig growth hormone gene by genetic engineering. It may well be that one of the family is a diabetic and has to regularly take insulin – the insulin will no longer be that isolated from pig carcasses but will be human insulin, again produced in a

fermentation system – perhaps by yeast cells, perhaps by animal culture cells. The cells will have had the human insulin gene introduced by genetic engineering methods.

One of the family may that day be joining the blood donor scheme and will have a test for AIDS by a test kit which has been produced by genetic engineering methods. That person also may be vaccinated against hepatitis, the vaccine in this case being a safe and efficient vaccine, produced by genetic engineering methodology.

Perhaps the mother in the family is pregnant and will that day be having an amniocentesis test which will enable screening of the foetus, not only for major chromosomal disorders as is currently the case, but which will also permit screening for a number of inherited diseases. The early detection of such diseases may sometimes warrant termination of the pregnancy but will frequently allow the correct early nutritional or other treatment to be given which will considerably ameliorate the effects of any such disease.

None of these things sound particularly frightening, in fact they obviously are going to be improving the quality of our lives. So what is it about genetic engineering that at some times and for some people makes them think that it is terrifying, whereas I would say it's terrific. Well, first of all let me tell you a little bit about what it is and exactly what happens. It is not, as many people think, the cloning of animals or parts of animals. The only cloning that is done in genetic engineering is the cloning of a specific piece of genetic message.

About 10 years ago the only way a person like myself could study a gene, from man or from a wheat plant, was to work with the whole population of genes in a nucleus. Now we have a lot of DNA, you may be interested that if we were to take all of the DNA that is in the cell nuclei of our body and stretch it end to end, that line of molecules would stretch to the moon and back several times. It really is an enormous total amount of DNA and even within one nucleus there is something like several hundred thousand genes-worth of genetic message.

So you can imagine what a blinding light it was when two things happened which enabled us to pick out a specific piece of genetic message and work with it. One of the two tools provided were enzymes which cut DNA at certain sequences coded along the molecule. These are called restriction enzymes which are used by bacteria to protect themselves from other pieces of DNA that enter through their cell walls. These restriction enzymes chew up foreign DNA, yet because of certain modifications to the recognition sequence they do not touch the DNA of that host cell. There are a whole variety of restriction enzymes and they have provided us with a series of precise genetic scissors.

The other major finding was that of small circles of DNA in bacterial cells. These are called plasmids. They have the ability to replicate, to multiply in the bacterial cell in large numbers. These, too, can be cut by genetic scissors in a controlled way! It's possible to join in other pieces of DNA in rebuilding that circular plasmid. By putting on one particular DNA segment we can multiply it up in a bacterial culture as much as we want and purify large amounts of the segment to study and use in various ways.

Those two discoveries sound very simple. They are. So simple and so important that each of them have won Nobel Prizes for their discoverers.

These days it's possible to read the genetic message of a piece of DNA very quickly. It is also possible to modify the genetic message in a controlled way, and for a number of animals and a number of plants it has been possible to take engineered DNA – isolated DNA segments – and

reintroduce them back into a living organism so that the gene segment is working properly and becomes part of the genetic blueprint or programming of that individual organism.

I think now it might be best if I describe to you some of the things that have been found out and give you an idea of what it is possible to do with these techniques.

Let me first talk about some findings with plants, which is my own research area. You may remember that last year Barbara McClintock received the Nobel Prize for work that she did nearly 40 years ago in which she deduced that there were certain genes in the corn plant, and probably in all plants, that did not have a regular place in a chromosome. Generally we think of genes being in a strict order along a chromosome. These special genes were able to move, sometimes with quite high frequency from one place to another. They are called transposing elements, or we might call them 'Jumping Genes'. For quite a long time little notice was taken of McClintock's seemingly heretic views, however, recombinant DNA technology has enabled us to confirm her conclusions and just a little over two years ago in Canberra we isolated the first jumping gene of maize. Thus the jumping genes are now a true physical entity and we have studied them a great deal, as have a number of other laboratories around the world; they are proving to be extremely useful in research. For example, since they can move themselves from one location to another in a chromosome, they presumably could help us to introduce genes back into plant chromosomes. If we were able to stitch in the gene we wanted to introduce into the middle of one of these jumping genes that we'd isolated, then it may well be able to provide us with a vector or vehicle for taking that gene into a target plant.

Another use is that when these jumping genes move around the chromosomes of an organism, if they land in the middle of a working gene they will inactivate it and turn the gene off. This causes a mutation and it provides us with a way of finding a gene which has a particular function. We can follow the jumping gene and when we find a mutation in the function we're interested in then we can go in, pick up the jumping gene and know that the sequence on either side of it is the gene we want. This has now been practised in maize and I anticipate will be used in many other plant species.

I've talked about the introduction of genes into plants. This has already been achieved in a number of plant species. It has been done in two ways. One way uses a disease organism, the soil bacterium that causes Crown Gall disease in a number of plants like peach trees, tomatoes, potatoes. This bacterium, we have found out by using recombinant DNA methods, regularly inserts a part of its chromosome into the plant chromosome and that's what causes the cancer – it's really an oncogene causing uncontrolled growth – the Crown Gall. We have been able to take that piece of DNA and remove the tumour-causing functions from it but use its other biological properties, that is the way in which the bacterium enters the plant cell and knows how to introduce the segment into a plant. So we now have a number of instances where a bacterial gene or another plant gene has been introduced into a target plant in a way that makes a stable addition of that gene to the plant's genetic make up.

I'd like to give you just one example of this process because it points out another extremely important phenomenon that we've learned about. The French bean, the bean seed that you eat, has a lot of storage proteins, and one of the major storage proteins in the French bean is called phaseolin – that's after the name of the bean plant. The gene coding for that storage protein has been isolated by recombinant DNA methodology and has been joined into the inserting region of the Crown Gall bacterium chromosome. It has, for example, been put into the tobacco plant which is used a great deal in laboratory experimentation because of its ease of culture. The important feature was that the gene did not work in the tissue that grew immediately after the

infection, nor did it work in the stem tissue of the plant that grew out of the infected callus tissue, nor did it work in the leaves or the flowers. The only time that gene was switched on was in the seed of the tobacco plant, which is where it normally functions; it operated at the time of development and in the tissue that it would normally work in the bean plant. What this has told us is that just in front of the genetic coding region for the storage protein gene there is a segment which contains the control switches which determine when that gene will be switched on, both in developmental time and in what tissues. This is very important because it means that if this is a general situation, and it certainly appears to be the case, it simplifies the task of the genetic engineer to introduce genes into a recipient target species. A lot of the correct control is automatically coded for in the segments immediately adjacent to the gene.

This is true too not only for genes that are switched on at a certain time of development but for genes that respond to certain environmental signals. In fact, if some of your cells are exposed to extremely hot conditions, most of your genes will switch off and only a certain array of them – so called heat shock genes - will be turned on. It has been shown that that is due to a particular switch region in front of the genes - the beat shock switch.

Plants have exactly the same response and in fact it's almost exactly the same switch code in animals and plants. There are other coded messages in plants which switch some genes on in leaves only when light shines on those leaves, which makes a lot of sense. You don't want some of the genes involved in photosynthesis working in the night when there's no sunlight – they only switch on when light actually shines on the leaf.

Just recently at a meeting in America I learned of another way of introducing genes into plants. This is where the DNA preparation can be allowed to pass through the membrane of a naked plant cell; the cell wall can be removed, to produce what is called a protoplast with just a cell membrane. DNA can enter through that membrane and become incorporated into chromosomes. For some plants, where a whole plant can be induced to regenerate from a single protoplast or cell – the protoplast will re-grow a cell wall and go into division again – this promises to be a very powerful technique.

The really quite fantastic things that we have begun to learn about plant genes and their properties, of their structure and the way in which their expression is controlled – all of this has happened in the last couple of years and is very exciting for a person like myself. Couple this with the ways of introducing genes into plants and you see that we're in the process of developing another method of plant breeding which will supplement the existing methods and make us better able to tailor plants to our needs. This is a very exciting prospect. For example, although recombinant DNA genetic engineering will probably be restricted for many years to the introduction of single genes, or at most a few genes, that still gives some hope that we will be better able to equip crop plants against diseases and pests and other problems where we know that single genes can be of importance. There's a long way to go but it's a very fast moving field.

We might also be introducing quite novel genes into plants. I want to give you one example. There's a bacterium which produces a protein that is a strong insecticide. In fact, this protein, inside the bacterial spores, is already sprayed in some agricultural operations, for example, to protect cotton crops against the moth pest *Heliothis*. It is a difficult process to produce enough of the bacterial spores and then all the conditions have to be just right in order to get an effective spray. What many labs around the world are doing now is to take the gene from the bacterium, the gene that codes for that protein, and it has been isolated, and introduce it into a plant so that the plant will make its own insecticide. Of course it would be ideal to equip the gene with a switch mechanism which switches on the gene only in the leaves, or in any other parts of the

plant we want to protect from insect attack. It's a very exciting possibility and is well under way in trials.

Perhaps I should now turn to some examples of what is happening with animals. The molecular biology of animal genes is even further advanced than that for plant genes. There have been quite remarkable discoveries. I always think that our current understanding of the mechanism of antibody production, the tremendous variety of antibodies that we produce to protect ourselves against foreign proteins, is a tourde-force of the recombinant DNA method; we now have an understanding of much of this process at a molecular level. It is interesting to not that this is one of the cases where nature has used jumping genes in a controlled way to produce a lot of variation. I can't go into that in detail tonight.

Recombinant DNA methods have also resulted in enormous increases in our understanding of the causes of many types of cancer.

We also now understand the basis of many inherited diseases. For many of the diseases that are associated with abnormal haemoglobin, for example sickle cell anaemia and thallasemia of one type or another, we now know precisely what error or change has occurred in the genes producing haemoglobin. Sometimes the change is in a single letter of the genetic code, one nucleotide altering the code for an amino acid in the haemoglobin protein. Sometimes the error is a much larger one, with a whole piece of the gene missing.

We also know a lot about the way in which animal genes are controlled, and again there are specific switch regions, specific control regions coded into the DNA, which cause many genes to be turned on or xeroxed in mRNA at particular times in the cell cycle or in particular tissues at particular stages of development.

This knowledge is helping us to design ways in which to treat diseases. We have at hand a great increase in our potential to diagnose certain diseases; some cloned genes can act as probes to determine whether an individual has a certain disease or not. I mentioned at the beginning of my talk the amniocentesis procedure which allowed certain inherited diseases to be scanned for in the blood cells of a foetus.

Apart from this great power of diagnosis there is the opportunity for therapeutic uses of recombinant DNA. On the one hand genetic engineering is being used for making better vaccines, especially in producing vaccines against disease where normal methods of vaccination have not been successful. We can now dissect a virus genome and find out which part of the genome is important in permitting vaccination against the disease caused by that virus. Hepatitis is one vaccine being produced in this way – it will come onto the market quite soon.

One can also ask about more direct gene therapy. What if we discover that an individual has an imperfect haemoglobin gene – can we overcome this imperfection by introducing a normal gene into the bone marrow cells? The answer would seem to be yes for a number of diseases. But this is where we immediately run into a high emotional context for recombinant DNA techniques. Should we be interfering and controlling the genetic makeup of man? Let me first of all discuss one or two issues about this. Are we able to introduce genes into animal cells? Yes, we can. They certainly can be introduced into cultured animal cells in the same way as for naked plant protoplasts, but that's really an experimental tool. We cannot grow animals back from cultured cells, whereas plants can often be grown back from single cells. If we wish to modify an organism and have that organism pass the gene onto future generations, then the modification, the addition of the gene, has to be in the germ line. Has this been done in any animals? Yes, it

has. It has been done, for example, with mice. One example is that a rat growth hormone gene has been successfully introduced into the chromosomes of a developing mouse embryo which then developed normally, reproduced and passed the gene on to future generations. If that gene is equipped with the right sort of control mechanism, then it can lead to the production of bigger mice than normal. But it depends on what switch gear is attached to the gene.

Scientists in CSIRO at Prospect here in Sydney are attempting to introduce genes into developing sheep embryos by this same sort of technology. You can see that if disease resistance genes could be added into sheep embryos then it could be advantageous for our wool and fat lamb industries.

What about humans? The technology is not yet developed for introducing genes into human embryos. We have no way at the moment of successfully introducing a piece of foreign DNA into a human embryo, although I believe that technically this does not present a huge task. I expect it could, and probably will be solved, in the next few years. I will come back to that issue and the ethical considerations that it most certainly introduces. But before I consider that I want to discuss the other general type of gene introduction into humans.

This is where we will introduce a gene into somatic cells, the body cells; the gene won't be passed on to future generations. It will only be a manipulation of the genetic make-up of the organism in particular tissues. There are already proposals being considered by authorities in the United States where it is proposed to introduce a normal gene to bring about an amelioration or cure of a disease caused by an imperfect gene. It is not yet possible to cure a number of the haemoglobin diseases because of the complex nature of the control of gene expression of these genes – that's another bit of knowledge that has come from the use of recombinant DNA techniques. But there are certain diseases where gene introduction may help. For example some you may have heard of the Lesch-Nyhan Syndrome caused by one deficient enzyme (HPRT – hypoxanthine-guanine phosphoribosyl transferase) in the body. It leads to a quite horrible disease. Fortunately it's rare. Any individual affected by this disease tends towards selfmutilation biting off fingers and lips and other extremities. These individuals have a miserable existence and usually have to be under extreme restraint. If we could introduce the gene coding for the normal enzyme into the bone marrow cells of the suffering individual it could bring about a cure. There are other examples where similar gene therapy may be a humane and effective answer to disease.

Let me consider a few of the questions which surround some of the prospects for recombinant DNA technology or genetic engineering. We certainly can be optimistic for the applications in developing new biotechnological industries. This applies to diagnostics for use in agriculture and veterinary medicine for example, and for the use of bacterial cultures, yeast cultures or cell cultures in producing proteins that otherwise are in extremely short supply. For human medicine there is promise of much increased diagnostic powers in the early detection of diseases. A corollary of this is more accurate genetic counselling. These all would seem to be highly acceptable in our society.

But there are other aspects that must be considered with regard to the increased diagnostic abilities. We may be able to determine that certain individuals are going to be prone to a late onset disease. Something that we really can't do now. A number of genetically controlled diseases have late onsets such as Huntington's chorea. We will now be able to tell by looking at the gene structure of a young person whether that individual is going to be prone to such a disease. Cystic fibrosis is another example.

Given that the potential for diagnosis is there, over what scale in the population should it be applied? Should we in fact be telling people that they will be prone to a late onset disease? Is it better that they don't know? Would such a diagnostic tool perhaps be misused in employment screens by potential employers? What about the way in which it might be used in determining insurance policy rates or suitabilities for insurance policies?

All of these questions are questions that must be faced. They have been met already for many similar issues. I don't think recombinant DNA technology is introducing any particularly new problems in this regard. But they are problems that have to be considered and talked out. Most of the control and cultural procedures are already in practice in our society and will be able to be applied to these new circumstances in the way that they have been applied to existing situations.

With respect to the ethics of gene therapy – this has been widely debated for many years and still needs to be further debated. I think it is very important to make the distinction between germ line intervention and somatic cell therapy in the way I have discussed. I believe that most of us would think it ethical to insert genetic material into a human being to medically correct a severe genetically caused disease. This form of somatic cell gene therapy does not have any different connotations, so far as I can see, from other medical techniques such as transplants. However, attempts to correct germ cells to enhance or improve a person by gene manipulation certainly would not have societal acceptance at present and perhaps it never should.

The other thing I would like to stress is that somatic gene therapy will certainly be constrained to single gene disorders for some considerable time. There is no possibility of approaching more complex attributes such as intelligence or physical stature or anything like that, with any such therapy. These characteristics have complex genetic and environmental determinants.

The ethical problems are not restricted to gene therapy with humans. We must also consider the regulatory controls for release of genetic engineered plants or animals into the environment. Are there any untoward hazards of releasing an improved plant cultivar where the improvement has been brought about by recombinant DNA technology rather than solely by other means of plant breeding? These questions are being considered in this country and other countries at the present time and once again we must seek a wide variety of opinion, these opinions hopefully being based on the best possible factual data.

Genetic engineering has become possible because of a number of substantial break-throughs. Its impact in basic biological knowledge is already profound and its applications in agriculture, industry and medicine are just being realised. Human gene therapy, if approved for use, will be applied to patients who have no better prospect for treatment of their disease, which is caused by a defective gene. This is not genetic engineering being applied as a eugenic tool to "improve" the human gene pool.

There are 2,000 to 3,000 human genetic diseases, and as many as two percent of newborn infants suffer from a genetic disease. At present for most of these diseases the defective gene has not been located and isolated, but we can expect rapid progress in this area.

Gene therapy has been successfully carried out in the fruit fly *Drosophila*, and laboratory mice. It should be possible to correct some specific genetic defects in individual patients. The major question seems to me to be when to begin clinical trials and not whether to begin them at all.

William Bateson, a prominent English geneticist, wrote in 1902 in this rediscovery of Mendells work "... Determination of the laws of heredity will probably work more change in man's

outlook on the world and in his power over nature than any other advance in natural knowledge that can be clearly foreseen". This statement has heightened emphasis these days with the advent of recombinant DNA technology. We can cut and stitch DNA segments no matter whether the segments are from plant, animal or micro-organism. We are now licenced borrowers of the books in the genetic libraries of nature.

In 1974 this science was born with a high degree of concern by the scientific community with regard to potential hazards of recombinant DNA molecules. This led to a lot of regulation surrounding experimentation. But it also resulted in a lot of work which showed that the concerns were somewhat naive and unsubstantiated. The risk assessment studies showed the techniques posed no special new and unanticipated hazards. We are now seeing consideration of risk acceptance with regard to the release of genetically engineered organisms. I believe there is still a danger of restrictive legislation, but hopefully regulations which will be formulated will avoid rigid legislation. We cannot afford to suppress the application of our new knowledge of genes and how they work. We, the scientists, are not "playing God" but critics who call for the abandonment of this technology may well be doing so.

CSIRO Division of Plant Industry,
Canberra, A.C.T., 2600,
Australia.

Return to Top