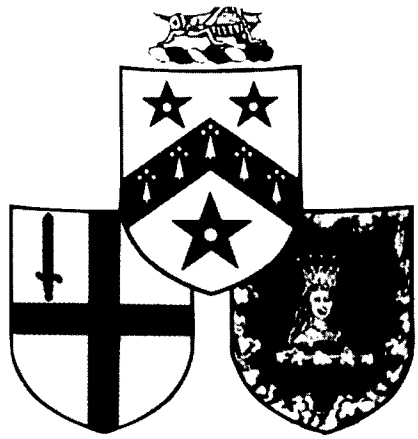
# G R E S H A M

## COLLEGE



# GENETIC ENGINEERING

Three lectures given by

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SECOND SERIES

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Genetic engineering: bioengineering of medical products

The first three lectures in this series, in which I outlined some of the principles and technology of genetic engineering, were largely concerned with the basic concepts of what can be done and how it can be done. During these lectures, I described how genes could be manipulated in such a way that cells produced what we wanted them to do instead of what they normally produced, a process widely known as genetic engineering or bioengineering. In these next three lectures I should like to consider how the techniques of genetic engineering can benefit the health of mankind, how genetically engineered products can be exploited profitably and, interspersed between these, why we are trying to obtain a map of the whole of the human genome.

Enzyme deficiencies

In 1765, King George III of England imposed a series of taxes which ultimately led to the American War of Independence and changed the history of the world to such an extent that the repercussions are still being felt today in places as far afield as Bosnia and Haiti. George III's actions were not rational and we now know that they were due to his medical condition, porphyria, resulting from a defect in the enzyme porphyrobilinogen deaminase. Today we could rectify this disorder by giving the patient this enzyme to compensate for its deficiency. Let us now look forward 20 years and the possibility of treating patients afflicted with Alzheimer's disease, also partly due to an enzyme deficiency, with a drug containing the appropriate enzyme. A doctor in a polyclinic might then be able to say to a patient 'the bad news is that you will have to take a tablet (or be given an injection) every day for the rest of your life'. In effect this would be quite acceptable and no different from the treatments now prescribed for high blood pressure, angina or diabetes. Could the actions of an irrational leader that precipitated the American War of Independence have been prevented today and is the simple treatment of Alzheimer's disease fact or fantasy? This is what this lecture is going to be about.

The contributions of bioengineered medical products to human health.

Health is a concept easier to describe than to define. Ill-health and disease are easy to recognise but come in a bewildering variety of forms: "all healthy people resemble each other, all unhealthy people are unhealthy in their own way", Tolstoy might have written and this creates many medical problems for there is no simple method by which all unhealthy people can be restored to health in the same way, every one has to be treated differently. The opposite of health is 'un-health' and this equates with disease and the various disease states can be recognised, described and categorised as (1) inbuilt errors of metabolism which occur when there is too much or too little of a substance essential for the correct working of the human body, (2) uncontrolled cell proliferation causing cancers and (3) infection by microorganisms of various kinds. All these disease states are under the chemical control of complex molecules, known as macromolecules, and all are theoretically susceptible to manipulation using the techniques and products of genetic engineering.

Currently, molecular geneticists are most interested in what are probably the easiest problems to solve, the inbuilt errors of metabolism. The human body is composed of cells and each cell is a factory making products some of which are involved in the day to day activities of that cell and others that are transported around the body acting as signals to other cells to perform their appropriate function. In healthy bodies, everything is carefully controlled

by enzymes and hormones. Enzymes are the familiar catalysts of biological systems that control the patterns and rates of chemical transformation. Food, for example, is broken down by enzymes into smaller components that can be absorbed and used by the body. Hormones are chemical signals of which the sex hormones, such as those used in hormone replacement therapy, are the most familiar. In healthy bodies, there is a delicate balance between enzymes and between hormones, both of which can be considered as regulatory proteins, many of which act antagonistically. Deficiencies or excesses of these substances can lead to disease or abnormal behaviour. Diabetics, for example, lack the hormone insulin, King George III lacked the enzyme porphyrobilinogen deaminase and it is gradually becoming clear that many common conditions, such as mental disorders and susceptibility to coronary heart disease, are due to hormone or enzyme imbalances. For many of the inbuilt disorders of metabolism, the possibilities of replacing defective or inadequate enzymes and hormones or modulating the effects of their excesses are straight forward challenges that are of great interest to, and are being tackled by, molecular biologists and biochemists. Some of the potential uses of regulatory proteins are listed in Table 1.

Table 1. Diseases in which regulatory proteins are likely to be of use

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| Cancers |
| Cardiovascular disease |
| Immunological diseases such as autoimmunity or immunodeficiency |
| Metabolic diseases |
| Respiratory disease |
| Reproductive errors |
| Diseases of the nervous system |
| Infectious diseases |
| Diseases of old age |

Infections could also be prevented or ameliorated by genetically engineered products. The main defence against microorganisms is the production of antibodies and these can easily and routinely be produced under artificial conditions. In addition, the protective immune responses that are elicited during an infection are controlled by hormones called cytokines and these can also be made easily and have great potential for the control of infections. Cell proliferation is another biological characteristic that is under chemical control and a number of substances, including cyclins that start or stop the process of cell division, are also likely to be useful in preventing or containing cancers.

The chemical nature of medically useful substances

Enzymes, hormones, antibodies, cytokines and cyclins are all proteins and can be obtained by extraction from living material. Insulin, for example, is obtained from the pancreas of pigs and cattle and the hormone clotting factors in human blood can be obtained from blood banks as can antibodies. However, such methods are expensive, potentially dangerous if human material such as blood is used and increasingly objectionable for various ethical reasons. On the other hand, being proteins, these various products are eminently suited to mass production either synthetically or by employing the techniques of genetic engineering. Proteins consist of chains of amino acids and these can be synthesised very simply by adding appropriate amino acids together in the correct sequence. However, one of the problems inherent in this technique is that the actual shape of the molecule produced may not be the same as the

native one and, as shape is important for hormone or enzyme activity, an alternative technique is necessary. Genetic engineering provides this alternative. Essentially the DNA that codes for a particular protein is extracted and inserted into the genetic make up of another cell in which it takes over part of the protein manufacturing machinery of that cell causing it to produce large amounts of the protein required. The recipient cells can be bacteria, yeast cells or mammalian cells and, once established, a transformed cell line can produce the desired protein in vast amounts indefinitely. Genetic engineering, therefore, has the potential for manufacturing products that can be used to replace deficient enzymes or hormones, artificial antibodies and also the reagents used for the detection and diagnosis of disease.

Medical products required

Let us now consider some of the products that are required and how far the techniques of genetic engineering have been successful in providing them. A partial list is given in Table 2. These products include hormones, enzymes, blood products, antibodies and cytokines. As well as proteins for therapy, there are also products required for various tests for the diagnosis of disease and the main requirements for such tests are that they should be quick, reliable and cheap. Pregnancy testing, for example, has reached a very high level of sophistication and relies heavily on the products of genetic engineering. These diagnostic techniques employ proteins to recognise other proteins and DNA to recognise other DNA and are likely to be as valuable to clinicians as the therapeutic substances themselves.

Table 2. A partial list of biomedical products currently being considered for production using the techniques of genetic engineering

Hormones
- Insulin
- Growth factors
- Gonadotropic hormones
- Calcitonin
- Erythropoietin
- Hormone releasing factors
- Reproductive hormones

Enzymes
- Urokinase
- Prourokinase
- Hyaluronidase
- Superoxide dismutase

Blood products
- Clotting factors
- Clot dissolving factors
- Anticoagulant factors
- Human serum albumin
- Factor VIII
- Factor IX
- Antibodies

Cytokines

Alpha interferon
Beta interferon
Gamma interferon
Colony stimulating factor
Epidermal growth factor
Tumour necrosis factor

When one considers how many products are used by the human body during day to day activities, this list may seem to be a very short one. The reasons why this should be are two fold; the perceived need for a product and the likelihood of success in producing it. Many genetic disorders are very rare and, although potentially interesting and of great concern to the sufferer, are currently unlikely to justify the expense of developing the product although this will probably change as more and more bioengineered products come on the market.

The use of transgenic animals

It is now a very simple procedure to insert a required length of DNA into a foreign cell and this procedure can be taken a step further by inserting the foreign DNA into the early embryonic cells of an animal so that when it grows up it produces the protein required as well as its own. Such animals are known as transgenics and considerable progress has been made using transgenic animals, for example cows can be made to produce human hormones that can be collected from their milk and it is expected that antibodies will soon be routinely produced in the same way.

Potential versus problems

If bioengineering has such tremendous potential why are there so few bioengineered products and why have many diseases not been cured? This is a very reasonable question and the answer lies in the fact that the science of bioengineering is still in its infancy. To quote from a World Health Organization Press Release dated March 1994

> 'Gene therapy is a technique that though still in its infancy, promises to be of great value in the fight against a number of diseases. It is useful to think of gene therapy as a way of using genes pharmaceutically comparable to any other form of pharmaceutical treatment. The technique can be exploited in several ways for a variety of diseases - to treat genetic mutations (as for cystic fibrosis); to kill a cell (as for cancer) or to modify susceptibility (as for coronary heart disease).'

In the field of bioengineering, practice lags a long way behind theory and everybody involved remains very cautious knowing that one false or premature move could set the whole science back possibly by decades. At present, the general public is ill-informed about what bioengineering is and what it can do and is also sceptical and concerned about its application. To some extent, the media, the pharmaceutical companies and the scientists are to blame, the media for spreading fear, the pharmaceutical companies for being overoptimistic and the scientists for both overstating their cases and for not informing the public adequately. There are good reasons to be cautious. Biologically important molecules are very complex and even the simplest of them requires multiple chemical modifications to make it safe, stable and satisfactory. There is also the expense of developing and marketing many of the bioengineered products; the growth hormone which will be referred to later costs $20,000 for a year's treatment. There have been unfortunate and

unforeseen dangers, bioengineered insulin, for example, is so good that diabetics have not had the necessary warning signs of imminent problems that were inherent in the use of pig or cow insulin. There are also numerous other problems that could not have been foreseen, the blood product Factor IX is effective in mice but not in other animals, some of the cytokines that control the immune response do not work in humans and many of the techniques used in animals are not appropriate for humans. Hidden costs represent another major problem; only about 1% of attempts to produce transgenic cattle are successful and the question is what to do with the remaining 99% of animals as it would be unethical and possibly dangerous to put them into the human food chain.

Human perception and legislation

There is a surprising amount of human resistance to the use of genetically engineered products, for example tomatoes genetically altered to enhance their keeping qualities have not been accepted and there have been many well-meaning but ill-informed campaigns to curtail this kind of development. If genetically altered tomatoes, bananas or orchids are unacceptable there is little hope for the universal acceptance of bioengineered medical products. In this context, it is interesting to note that many of the public are prepared to accept products made from foetal tissue but not from genetically engineered material. Here, there is a considerable degree of ignorance that should be put right by education but there is an overall reluctance to invest in this. Legislation is necessary to control the use of bioengineered products but restrictive legislation has gone too far and is presently slowing down or shackling attempts to produce and use bioengineered products. This problem can be illustrated by reference to a recent case in the United States in which a trial of human growth hormone in children of short stature had to be halted because a suit filed in the US District court in Columbia argued that the trial violated national rules for using children in clinical studies by needlessly risking patients' psychological and physical health. If children cannot be used in such a trial, growth hormone therapy cannot be evaluated and has no future.

The future of bioengineering

It cannot be denied that everything that we are or do is controlled by our genes whether we like it or not. The effects of some of our gene products are very easy to see and to understand, the absence of an enzyme or hormone for example, others are much more difficult to understand and these include such human characteristics as intelligence. If bioengineering is to have a future, its practitioners must realise that the public has a right to products that improve health but that interfering with the human genome in other ways is something that must be avoided. The future of bioengineering lies both in increased awareness on the part of the public of what is and what is not possible and, on the part of the scientists, what the public is prepared to accept.

We do have a long way to go and the present situation can best be summed up by statements from the World Health Organization and from the scientific journal Nature.

> 'Rapid advances in genetic technology are bringing a cure for haemophilia within reach, according to a World Health Organization group of international experts. The first cases of cure of the disease through the technique of gene therapy will be achieved, given essential further developments, by the end of the decade, the experts predict.

> Haemophilia is the most frequent inherited disorder of blood coagulation and causes a life-endangering tendency towards excessive bleeding...and affects one male in every 10,000 in the general population and is currently treated with the transfusion of blood products which contain the clotting factors that are deficient in haemophilia sufferers'.
> (World Health Organization, March 1994)

> Clearly the gulf between the laboratory and the patient remains deep. But already the first stirrings of a revolution can be seen. ... Take, for example, the ability to select from ... random peptides the one that can block the growth of Staphylococcus, antagonise one class of enkephalin receptor or lower blood pressure. Will not the search for new drugs shortly be changed out of all recognition? None of these developments is yet in clinical use, and none is free from problems. Indeed, it is now clear that many of the hopes and expectations with which the search for 'gene therapy' began were unrealistic. But that in no way invalidates the medical potential of molecular biology. Rather, it is now plain that the dedication of the pioneers in the field has started an advance that will one day be able to improve the existence of everyone on the planet'. (Nature, December 9th 1993)

The future of bioengineering is now on a steady course and provided that there are no false promises, no attempts to get rich quick, no uninformed obstruction and a will among scientists and clinicians to work together on an international basis instead of against one another then the future is very rosy. However, these are big assumptions but there is evidence that all will be well as far as the scientists themselves are concerned and evidence for this comes from the massive international collaborative programme to map the whole of the human genome which I will discuss in my next lecture. Thereafter it is up to the pharmaceutical companies and others to make a profit and this is something I shall discuss in the third lecture.

Genetic engineering: the human genome project

On Tuesdays I work at the wellcome Trust where above my pigeon hole is one simply and boldly marked HUGO. Who or what is HUGO? HUGO is, in fact, an acronym for The Human Genome Organization which was set up in 1989 to coordinate the activities within the world-wide Human Genome Project. This is a collaborative effort, organised by scientists, to coordinate research on the human genome, to foster collaboration between scientists and to integrate this research with other scientific, social, ethical and commercial activities. HUGO exists for scientists, it is a bottom-up organization serving the scientific community and unburdened by layers of bureaucracy. Because of the way it is run, HUGO is very efficient and has adopted a very low profile. However, this low profile masks the most ambitious scientific project ever undertaken; nothing less than to map the whole of the human genome (the sum of all the human genes). Tonight I am going to talk about what the human genome project is, how it sets about its work, what progress has been made and what the long term aims for the future are.

The beginning of the human genome project are shrouded in mystery and controversy. Many believe that stemmed from an article in The Lancet in 1979, the brain-child of two British scientists, Walter Bodmer, of the Imperial Cancer Research Fund, and Sydney Brenner at Cambridge. Others believe that the project had its roots in the United States in 1985-1986 when the University of California, the Department of Energy and the National Institutes of Health started what had now become the most successful example of scientific collaboration ever envisaged and currently involving scientists in 36 different countries including the People's Republic of China. One might argue indefinitely about priorities but there is no doubt that the money and effort put into the project by the United States could not have been matched elsewhere and the skills and perseverance of the British scientists have ensured its success from the very start.

The human genome

I have said before that everything that we are or do is controlled by our genes that are nothing more than lengths of DNA consisting of sequences of four nucleotides, adenine, thymine, guanine and cytosine always referred to by their initial letters A, T, G and C. In the controlling centre of a cell, the nucleus, DNA exists as a double strand in which A in one strand is always linked with T in the other and G with G. These A-T, C-G pairs are known as base pairs. The proteins that make up the structure of our bodies and the enzymes and hormones that control our various body functions consist of various sequences of amino acids out of a pool of 20 different kinds. Each amino acid is coded for by three nucleotides, for example the amino acid leucine is coded for by the DNA nucleotide sequence GTT and glycine by CCT. A gene is a functional length of DNA, that is, it codes for a recognisable protein product such as an enzyme. Humans possess about 100,000 genes representing 3000 million base pairs and if the whole of the human blueprint were to be written in the four letter nucleotide code it would fill 134 sets of the Encyclopedia Britannica or 3000 Mb of computer memory. In passing, it is amazing that, in most of us, this blueprint is always translated without any errors. In the nucleus of the cell, the strands of DNA are coiled, supercoiled and condensed into chromosomes which are the only part of the genetic make up that we can actually see with a microscope and handle with ease. Humans possess 22 pairs of chromosomes plus one X and one Y in males and 2 Xs in females giving a total of 46 chromosomes.

Mapping the human genome

The chromosomes are the starting points in any attempt to create a gene map. In order to explain the complex procedures involved in mapping any gene it is probably best to start with a simple model. Imagine an archipelago with 46 islands, 22 of which have identical sister islands and one X shaped and one Y shaped island. On one island lives a shoemaker and you want to track him down and pinpoint his actual address. You will need to know which island he lives on, which street his shop is in and which shop in that street is his. One can do this by following a number of clues, watching the import of leather, for example, or the export of shoes. Gradually the target can be narrowed down by constructing a number of maps of increasing detail, for example, the island, a street map and a street directory. This is the basis of the human genome project, the shoemaker represents the gene, the house represents the exact position of the gene, the street represents the stretch of DNA containing the gene (the post code or zip code) and finally the island which represents the chromosome. There are also other analogies between the shoemaker and the human gene. The shoemaker (the gene) holds the instructions for making shoes, he (or she) imports leather, cotton and nails (amino acids) and exports shoes (the protein product). If shoes started to come out with a major defect, the source could be traced and the defect rectified. This is essentially the aim of the human genome project; to map the human genome so that defects can be identified and rectified.

How the genome is mapped

Genes are not shoemakers so we need to return to hard science. For many years it has been known that certain characteristics are inherited and that some of these are associated with gross changes in the chromosomes. In Down's syndrome, for example, there is an extra chromosome 21 and in other conditions parts of chromosomes are missing or displaced. Evidence also comes from other directions, for example, because males only possess one X chromosome, certain defects that occur in males and never in females can be traced to this chromosome. The fact that identical twins possess identical genomes also provides vital clues as do familial studies. Using all this kind of information and recognising that certain characteristics are inherited together, suggesting close proximity of the genes involved, it is possible to construct low resolution maps. By the beginning of the 1980s relatively few gene positions had been mapped and these were the most basic coding for such characteristics as eye colour, blood groups and gross deformities and disorders.

Obviously, such an approach could never product the sort of gene map required by geneticists so clues were accumulated from other sources particularly the laboratory mouse. All mammals are basically similar and the mouse is a convenient model to use as it is possible to breed lines of mice that are genetically identical (as are human twins) and from cross breeding experiments with these it is possible to study differences caused by a single gene. A vast amount of information about the genetic control of the human immune system, in particular the acceptance or rejection of organ transplants, has been obtained from mice. Mice, however, are not humans and valuable as the clues they provide may be, they are only clues.

It is therefore necessary to take a more direct approach and this has been made possible by recently developed techniques such as the yeast artificial chromosome, commonly known as a YAC. Yeast cells can accept a vast amount of foreign DNA. Using the techniques of gene cloning, sequences of human DNA can be inserted into the yeast genome in which they are replicated as the

yeast cell divides providing ample material for detailed study. By taking many different sequences and overlapping them so that they align correctly, like the use of tree rings for dating wood, it is possible gradually to build up long sequences that actually represent genes of interest and adjacent genes. This technique was once very laborious, time consuming and with a fail rate of over 4% but can now be done quickly automatically by machine at a cost of about $0.50 per base pair although there is still an unacceptably high fail rate of 0.1% and this can lead to a lot of unnecessary duplication of effort.

Having determined all the sequences of nucleotides that constitute a normal genome it should be possible to screen for defects caused by mutations which can be seen as substitutions of one or more nucleotides by others that cannot code correctly for a particular produce. Such screening involves comparing the normal sequence with the abnormal one in a manner analogous to that used by spellchecks in word processing programmes.

The division of labour and progress so far

In order to ensure the optimum use of resources and to avoid unnecessary duplication, particular laboratories have been allocated individual chromosomes or parts of chromosomes and newcomers can be integrated into the programme by becoming involved with the efforts of existing groups. Progress is charted by regular meetings devoted to individual chromosomes and has been very rapid. The years 1991-1995 have been mainly concerned with perfecting the necessary techniques and beginning to accumulate data, 1995-2000 will be devoted to collecting more data and 2000-2005 to consolidating the data and producing the complete map. So far, an overall map has been produced which shows the various key landmarks, chromosomes 21 and X have been practically mapped and a complete map of chromosome 6 is well under way. Everything seems to be going according to plan.

Purpose of the project

The human genome project has one major aim and this is to map the positions of the genes responsible for 4000 or more genetic defects. This should enable scientists and clinicians to correct defects, predict possible defects and to warn individuals about predisposing factors. It will be some time before the replacement of defective genes becomes a reality and it may be that, although possible, the rarity or expense of correcting some disorders will never be achieved. The accurate prediction of defects should give parents an opportunity to consider the termination of a pregnancy or even warning couples not to consider conceiving a child but this leads us into social and ethical problems way outside the experience of a scientist. Avoiding predisposing factors is a simpler possibility. Many diseases are caused by external factors but predisposition to them is genetically controlled. Among such diseases are coronary heart disease and respiratory problems such as asthma. Those carrying the gene could be warned not to smoke, for example, or to avoid contact with certain substances or environmental conditions. The human genome project has already made an important contribution to this subject with the discovery of a mutated gene on the short arm of chromosome 2 strongly linked with colon cancers. 70% of those with the gene will develop colon cancer but the knowledge now available means that regular screening by colonoscopy will reduce the chances of the disease progressing to an incurable stage.

Problems for the future

The possibility of ethical problems has already been mentioned but the

problems go further than this. There is a Yorkshire saying that goes something like 'where there's muck there's brass' but I would reverse this and say 'where there's brass there's muck' and there is real brass in knowledge of the human genome. This is going to become a multi-million dollar industry as pharmaceutical companies and others vie with each other to perfect gene replacement therapies and to devise the various diagnostic tests that will soon become commonplace. The possibilities for making money are myriad; patents for one. Currently there is a great debate about whether it is possible to patent a gene and this leads to such questions as whose gene is it anyway and who owns a body after death if his or her cells still survive and are kept multiplying. Currently the criteria for patenting a gene is worded along these lines 'A DNA isolate comprising a continuous sequence encoding [X] depicted in Figure [Y].' Patents do not, however, permit errors and there has already been one case in which a simple typing error has made nonsense of a patent application. In this case the patent application for cartilage inducing factor beta read Gln in position 12 instead of Glu. Gln is the standard abbreviation for the amino acid glutamine and Glu represents glutamate. The applicants, thereore, lost the chance to patent their discovery because of a simple typing error.

There are also other problems some more immediate than others. Already insurance companies are considering ways in which they can gain access to genetical information in order to increase premiums or even to refuse cover to certain individuals altogether. In September 1993, representatives of leading European insurance companies met in Paris to consider 'how they could head off legislation aimed at restricting their access to genetic information about those seeking insurance cover'. Some governments have already taken a stand about this, in Denmark seeking or attempting to use such information is illegal and in the United States there is a temporary moratorium on seeking and making use of such information. There is no doubt, however, that where money is concerned, ways around such protective legislation will be found and insurance companies will be able to discriminate as they already do against smokers, for example. At the end of the day, nobody can force an insurance company to insure them and the failure to reveal genetic information may soon become a reason for the non-issue or invalidation of a policy. Finally, there is the problem of the 'snake oil salesman', the purveyor of spurious tests and cures. The frightened, ignorant or merely gullible are all at risk as the actual disease or condition may not be immediately apparent.

Problems like these will abound once the human genome project has left the safe custody of the scientists involved in it. The scientific community has set an excellent example of cooperation and integrity but the big question is whether or not the commercial world can act as responsibly and this is something I will discuss in my next lecture.

Genetic engineering: genetic engineering for profit

The central dogma of molecular genetics states that DNA makes RNA makes protein to which the cynic might add makes profits. The question is, who makes the profit? Is it the scientists who make the discoveries, the companies that produce and market the product or those like lawyers and insurance brokers standing on the sidelines? Before castigating those standing on the sideline, who may well be considered as vultures, it should be remembered that vultures do a very useful job in clearing up the mess left behind by others and both scientists and pharmaceutical companies do leave a lot of mess that has to be cleared up by someone.

The commercialisation of genetically engineered products is not a new phenomenon and throughout human history there are records of man's attempts to breed better and better animals and plants and to profit from them by selling them on to others. One has only to go into a garden centre to see how many packets of seeds represent the commercial edge of countless breeding experiments. Improvements do have inbuilt costs and these costs must be passed on to the consumer and the profits ploughed back into future improvements. This is sound commercial practice but what is different about genetically engineered products is that progress has been so fast that it is almost impossible to keep up with developments let alone evaluate their commercial potential. The commercialisation of genetically engineered products represents a new venture in which rules have to be developed as the field develops and here there are strong parallels with information technology.

How big is the cake?

The potential for genetically engineered products is massive and by 2005, the end of the human genome project, is estimated to be worth at least £60-100 billion. The requirements for such products stem from a variety of sources. Multinational pharmaceutical companies need new products and replacement products for those made obsolete by the techniques of genetic engineering and, in this context, it is important to note that many of these new products are designed to cure or prevent diseases thus limiting the profits to be made from repeated treatments for chronic or recurrent conditions. Health providers also need better, safer and cheaper products thus there will be competition to provide what is required at an affordable price. This is likely to change the nature of the pharmaceutical industry completely because the present policy is for individual companies to rely heavily on a few high income products and not to compete too much in what they perceive as the less profitable fields.

What are the products required?

The obvious requirements are for the replacement of defective genes providing or replacing missing or malfunctioning gene products and reagents for the early diagnosis of disease or predisposition to disease. From the point of view of the medical profession and the patient there should be available something appropriate for every condition but from the commercial viewpoint this cannot be seen as a viable or profitable option. Take the replacement of defective genes, gene therapy as it has become known, for example. Altogether there are some 4000-5000 genetic disorders and this number may double as more and more knowledge becomes available. In the United States there are 60,000 patients with haemophilia, 30,000 with cystic fibrosis and 100 with adenosine deaminase deficiency. The first two of these may seem large figures but seen within the context of a total population of 250 million

they represent less than 0.035% of the population in which the most common diseases include coronary heart disease, which may affect up to 25% of the population, and cancers. One might argue strongly for gene therapy for haemophilia but the case is more difficult to make for adenosine deaminase deficiency, the only situation in which gene therapy has so far been tried. The real problem is that coronary heart disease and cancers together with arthritis, asthma and Alzheimer's disease are multigene disorders, in other words the problem arises from the interactions between a number of genes and not only one thus any possibility of gene therapy becomes increasingly difficult. Currently over 600 genes are being investigated for their possible involvement in coronary disease which gives some idea of the magnitude of the task ahead. There is also a conflict between rectifying the disorder or treating it and it is likely that the medical profession and the commercial organizations, many of which rely on repeat prescriptions, will see this problem from quite different perspectives.

Treatment by replacing defective products is another matter and insulin is an excellent example of how such treatment can work and genetic engineering has made it possible to produce large amount of pure insulin without recourse to animal products. There have been setbacks, some diabetics have not been able to detect early signs of problems with which they had become familiar using animal products, but tragic as these may have been, they are only likely to be temporary and the future for genetically engineered insulin looks very bright. Antibodies can be produced easily from cell lines and in time these will replace those extracted from human serum thus eliminating the minute risk of infection with viruses. Similarly, the cytokines that control the immune response are gradually becoming available and, although there have also been disappointments and setbacks, their use is almost certainly going to become routine within the next few years. Vaccines also come into this category and whereas currently there is no vaccine that is 100% safe and effective genetically engineered vaccines are gradually coming on to the market and, although still expensive, are proving to be safer and more effective than the ones they are replacing.

The most promising area of activity is in the development of reagents for diagnostics. There is currently a great need for the early diagnosis of many diseases, for example, signs of cancer, prediction of genetic disorders and the presence of infection, and the tests currently available are not entirely satisfactory in terms of speed, accuracy and cost. Rapid and accurate diagnosis is likely to be an essential component of the polyclinics of the future in which a patient will be able to see a general practitioner, a consultant and have a diagnosis made during a single visit.

Involvement of the multinational companies

Until about 1980 there was little interest in genetically engineered products but by 1987 there were over 700 companies involved and over the past few years the major international giants such as Ciba Geigy, Glaxo and SmithKline Beecham have all become major participants.

First let us consider the American experience. In the United States the commercial possibilities of genetically engineered products were realised early on and began as a spin-off from the research being done in academic institutions and resulted in a massive investment of 50% of the national academic research budget in the life sciences. In 1991 the National Institutes of Health invested $2.9 billion. Major commercial organizations such as Shell and Hoffman La Roche began to place contracts with academic

institutions and this produced advantages all round; the scientists saw the possibilities of working with excellent facilities and earning high salaries and the companies themselves were able to reap the benefits of not having to set up expensive research and development departments and avoiding the need for long term commitment. Gradually, the contacts became increasingly flexible and a number of biotechnology companies were set up to act as go-betweens linking the work done in academic institutions with the needs of the multinational companies. The result has been that many small, specialised and dedicated companies have been able to survive and thrive.

In contrast with the United States, the beginnings of the commercial involvement with genetic engineering in Europe were very shaky and the policy has been one of 'watch and wait'. Despite the fact that the European Union recognises that biotechnology is one of the major technologies offering significant advances to member states, in Europe as a whole the investment in research in the life sciences is currently only 30-35% of the academic research budget.

British involvement

In Britain, the situation is not at all promising and as recently as March 1994 Stephen Dorrell, Financial Secretary to the Treasury, stated that '..Government intends to launch an enquiry into relationships between biotechnology, industry and the City.' Note the use of the word 'intends'. Informed commentators are concerned that the City has adopted a 'quick buck' approach to the possibilities of a technology which by its very nature has a long lag phase of anything up to ten years before an idea becomes a product. The respected accountants Arthur Andersen note that in the United Kingdom biotechnology companies tend to be small and numerous; currently there are about 170, a quarter less than 5 years old and two thirds less than 10 years old. Arthur Andersen estimate that in 1994 the annual turnover in Britain will be £185 million and by 1995-1996 it will approach £320 million, an increase of 64%. These figures pale into insignificance when compared with the estimated world market of £26 billion by the year 2000 and more than double this figure by 2005. Despite having some of the best life scientists in the world, Britain will by then have less than 2% of the world market - less than that of countries such as Singapore and Taiwan.

The situation in Britain can be best illustrated by a consideration of specific case histories. In 1989, the University of Oxford gave £350,000 (then the price of a four bedroomed detached house in North Oxford) to a small biotechnology company employing three people. Oxford Molecular, as it has become, now employs 30 people and is worth £3 million. It operates by cooperating with other universities, including Cambridge and University College London in the United Kingdom and Strasbourg and the Paris Ecole Polytechnique in Europe, in the computer design of drugs. British Biotechnology is a company which was floated on the Stock Exchange in 1992. It is worth £150 million, employs a staff of 300 concerned with inflammation, cancer, asthma, vascular diseases and AIDS and has six products in the pipeline. Celltech, in Slough, is one of the biggest biotechnology companies in Europe. It began in 1980 and is mainly concerned with immunological-associated disorders including arthritis, autoimmune diseases, septic shock and some forms of cancer. Currently it has seven products in the pipeline. Celltech employs 410 staff, 234 of which are science graduates of which 100 have PhDs. However, it is felt that Celltech is too small and lacks the essential critical mass required for a sound future so it is considering closer relationships with a larger company.

The picture in Britain is of small, specialised companies producing a limited number of products targeted at major diseases. Such companies are unlikely to make a major impact on the world scene and there is the real danger that scientists will continue to leave this country to work elsewhere where the pond is bigger and working conditions, prospects, intellectual challenges and financial rewards are better.

In the future Britain may well miss out on the prospects of a world turnover by 2005 of over £100 billion per annum, half of which will be returned to research and development. One product alone, erythropoietin used in the treatment of kidney transplant patients, has potential sales of at least $1 billion per annum and a lifetime prospect of earning over $100 billion. The prospects for major companies and the shareholders who have invested with the major players are very good but these companies are very unlikely to be British.

The lawyers

Whereas the prospects for British scientists are poor, those for lawyers and others on the fringe of the genetic engineering revolution are much better. Already, there is great debate about whether or not life forms can be patented and the argument revolves around the concepts of discovery versus invention. In order to patent a product, an inventive step must be incorporated into the process and products that cost millions of pounds to develop will be cheap once the inventive step has been incorporated. The battle has turned away from discovery to the development of novel ways to make the product more cheaply, more safely or simply differently. This is a fertile ground for patent lawyers. Once a product capable of reproducing itself has been marketed, who owns the right to use the offspring? In the United States it has now been established that a farmer has the right to use the seeds from specially developed crops but it has not yet been decided who has the rights to use a particular cell line. The problems here are similar to those encountered with computer software, the costs are in the development but once marketed the product can be reproduced cheaply by others. The legislation that is aimed at preventing software theft is not in place for biological material and may be very difficult to devise. There have already been problems. The Harvard oncogene mouse, a strain of mouse especially susceptible to spontaneous cancer, has been developed and was awarded a broad patent in the United States in 1988. However, the European Pattern Office refused to patent this mouse, a decision that was subsequently overturned following an appeal. Both the British Medical Research Council and the American National Institutes for Health have filed patents for human DNA sequences but these have been rejected in the United States and Europe. The importance of such decisions lies in the fact that a knowledge of DNA sequences is essential in the development of DNA-based diagnostic techniques for which the world market is immense. SmithKline Beecham have already paid $100 million for access to such data but such responsible companies would not be happy if others simply used the data without paying those who generated it.

The whole area of patents with respect to genetically engineered products is a very happy hunting ground for lawyers and a very expensive one for the companies concerned with protecting their patents. It is estimated that defending patents adds more than 10% to the cost of developing any product, money that would be much better spent on research and development. There are also signs that these costs will escalate because there are different patent laws in Europe, the United States and Japan and, despite considerable pressure, GATT has not yet come to terms with the problem.

The insurance brokers

Within ten years it will be possible to determine the whole of an individual's genetic make up from a single cell such as a root hair or washings from the mouth. This will be done non-invasively and cheaply and, with great precision, it will be possible to make predictions about that person's health risks and longevity. Insurance companies are already anxious to have access to such information and the possibility of differential premiums is a real one and one that has already been implemented for a number of groups such as smokers and, in other areas, those living in buildings at risk from subsidence or those driving fast cars. No organization outside the insurance companies has yet come to terms with the implications of research into the human genome and the various techniques devised to predict genetic disorders. It is unrealistic to assume that the insurance companies will not try to be selective about those that they insure and those that they will not. It may well be that only those with no potential medical problems will be able to obtain life insurance or private health cover and it may even be that occupational pension schemes will exclude particular individuals. A possible long term effect could well be a two tier system containing those fortunate ones who are healthy and insured and those less fortunate who are not. The possible burden on the State is immense. There is also another aspect to this and this is that insurance companies, or those involved in occupational pensions, will force people to obtain genetic information that they would rather not have. A real possibility is a young woman being told that she is going to develop breast cancer but that the company won't insure her. Complacency is not going to help, we only have ten years to go.

Espionage

The relevance of genetic profiling and the technology associated to espionage has not even reached the realms of fiction but is a real possibility. Information from a single cell, for example from a hair left on a comb or hairbrush or even skin cells brushed off one's back could reveal all that someone wanted to know about the health of a head of state, a political leader, a business rival or a prospective marriage partner for oneself or for one's son or daughter. However, I am now moving into uncharted waters and I leave these ideas to your imagination.

Epilogue

Orwell's 1984 came and went peacefully but will the 'brave new world' of 2005 be so uneventful? As far as the world of bioengineering is concerned, I doubt it very much.

# *GRESHAM COLLEGE*

## Policy & Objectives

An independently funded educational institution, Gresham College exists

- to continue the free public lectures which have been given for 400 years, and to reinterpret the 'new learning' of Sir Thomas Gresham's day in contemporary terms;

- to engage in study, teaching and research, particularly in those disciplines represented by the Gresham Professors;

- to foster academic consideration of contemporary problems;

- to challenge those who live or work in the City of London to engage in intellectual debate on those subjects in which the City has a proper concern; and to provide a window on the City for learned societies, both national and international.

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