Session 1

The Twentieth Bawden Lecture

Chairman	Mr J NORTH
Speaker	Professor J HILLMAN
Session Organiser	Professor D ATKINSON

BIO-ENGINEERING - INTELLECT, ENTERPRISE AND OPPORTUNITY

J.R. HILLMAN
Scottish Crop Research Institute, Invergowrie, DUNDEE, DD2 5DA

ABSTRACT

In this article I explore the benefits to mankind of various kinds of technology used to introduce new characteristics in living organisms, and consider the issues arising from the creation of new life forms. Bioengineering in its broadest definition includes engineering required for various methods to synthesise animal, plant and microbial products, and also includes devices to assist in the functioning of the human body. Recombinant DNA technology - genetic engineering - is the ultimate engineering, however, allowing mankind both to explore the very processes of life and to exploit the intellectual products. The subject matter encompasses a vast literature, replete with jargon and complex concepts. It is also one of the most rapidly advancing, innovative areas of science, worthy of substantial investment by private industry and by government alike. We live in the age of the biologist.

INTRODUCTION

Last year, Professor C. R. W. Spedding presented the nineteenth Bawden Lecture, choosing as his topic the role and impact of technology, legislation and public opinion on modern agriculture. He noted that effective demand has the dominant impact on modern agriculture, and that technology is essentially an enabling procedure constrained by legislation, need and economics.

This paper focuses on technology of a special kind - variously referred to as bioengineering, genetic engineering, recombinant (r)DNA technology, genetic manipulation, genetic modification, depending on the sort of image that is meant to be conveyed. When applied to genetics, "engineering" has a strongly negative image in the minds of the public, many politicians and pressure groups; it indicates unnatural procedures with potentially calamitous risk. In my view, bureaucratic obfuscation, euphemisms, undue sensitivity, secrecy and dithering are no substitute for an open clinical approach to risk assessment, and recognition of the sheer brilliance and potential of the technology. It cannot be de-invented; it must be exploited responsibly. The need is pressing.

Genetic engineering currently has its greatest applications in pharmaceuticals and drug design. Studies on catalytic and other antibodies, human gene therapy, the Human Genome Project and drugs whilst being anthropocentric nonetheless mutually interact with related studies on plants, fungi and microorganisms to advance knowledge in the whole of genetic engineering. I shall concentrate on crop plants, the underlying theme of this Conference, avoiding as much as possible specialist vocabulary.

IE NEED

griculture in Developed Countries

From the perspective of most members of the public in the western world, griculture is not viewed as a priority topic. In fact, its importance is derstated. Most references to economic analyses in agriculture and orticulture relate simply to gross traded values of commodities, hectares own, yield estimates, major categories of land use, imprecise crop and vestock categories, unit prices, direct employment and percentage origin of oss Domestic Product. Data relating to (i) processing values for the food d non-food sectors; (ii) development and maintenance of rural, industrial d marketing infrastructures; (iii) amenity and tourism; (iv) influence of bsidies; (v) costs of import substitution; (vi) assessments of trends in and ospects for exports and trading; (vii) relative social values to the tional and local economies; (viii) cultivar performance and market share; d (ix) indirect employment, are usually ignored because they are often reliable, incomplete, out of date, anecdotal, disputed or subject to mmercial secrecy. International comparisons are made especially difficult variations in the methods and dates of sampling, unspecified types of alyses and fluctuating currency exchange values. As a general point, it is rmane to note that arable and horticultural crops produced in the UK had an nual value of £6,527 billion in 1990 (1.4% of Gross Domestic Product) before dustrial processing and value-added contributions. During the past three cades there have been dramatic, research-driven, improvements in commodity ocessing, crop productivity and efficiency throughout the world.

Within Europe, public and political opinions of the effects of the Common gricultural Policy of the European Communities tend to relate to unwelcome anges to the countryside, expensive food surpluses/stockpiles, subsidies, otas, set-aside land, extensification, restrictions on pesticides and trogenous fertilizers, undignified animal welfare, and reappraisals of R&D iorities. All in all, opinions are not favourable towards agriculture, though the products are a basic need and civilisation is agriculture-pendent.

pulation Pressures

A billion extra people are projected to be added over the next ten years the world population which presently exceeds 5.4 billion (see annual ports from the World Commission in Environment and Development; FAO, World sources Institute and Worldwatch Institute). Inordinate strains will be aced on the less-developed countries for food, water, shelter, fuel, ducation and welfare. Large parts of Africa, especially, face dismal ospects. Access to the media and advanced medicine, though, will ensure at all citizens will demand improving quality of life regardless of local conomic situations. Low-grade grazing systems coupled to poor, unsustainable gricultural systems will inexorably lead to the acceleration of forestation, soil erosion, desertification and the rapid loss of natural and naged ecosystems, destroying genetic and environmental diversity. Social stability, emigration and trade disruption seem inevitable for the poorer the less-developed countries.

Largely as a result of major if unsung technological successes in the cent past, especially in plant breeding and pathology, agriculture and e related life sciences are universally assumed to be able to adapt without jor investment to meet the challenges of population growth. At the same

time, it is expected that agriculture should not adversely affect the natura flora and fauna, nor exacerbate any potentially undesirable effects ("climat change") of the changing gaseous composition of the atmosphere since th advent of the Industrial Revolution.

It seems remarkable that there is so little publicity given to the los of cultivated land throughout the world. Soil erosion, pollution, buildings roads, airports, and recreation facilities account for the main loss o productive land. Modern monocultural agricultural systems can cause problems e.g. use of xenobiotics, soil compaction and erosion, salinity effects an changes in the soil flora and fauna, but traditional methods (e.g. slash-and burn, uncontrolled grazing) can be even more erosive without even bein productive. All too frequently, third-world agriculture can incorporate man of the bad practices of high-input agriculture now being phased out in th western world. About 85% of the growth in population occurs in developin countries where the numbers of malnourished people have increased by 35% sinc 1980. In the tropical zones, the area of cultivated land per capita ha declined from 0.28 ha in 1971 to 0.22 ha in 1986; this figure mask urbanisation, fragmentation of farms, and expansion of cultivation into virgi lands unsuitable for arable farming in the medium term.

Given that the area of land under cultivation is a limited resource an difficult to increase without massive migrations of people and devastation o forests, that pests and diseases have a phenomenal ability to circumven control measures, and that research and development demand long-ter commitment, the global picture is far from bright until the demand of th world population matches sustainable resources.

One possible or probable scenario is that the industrially under-developed - or low income - world will become the major source of manufacture goods, effectively reversing the trend in trade established since th Industrial Revolution (Carruthers, 1993). The economies of most of th countries of the Pacific rim are buoyant, and in Asia there are severa countries with sophisticated, urbanised workforces able to operate efficientl and compliantly with relatively low incomes. Scientific intercommunication multinational trading, and improving education in the low-income world ensur that invention, intellectual property and service industries will not be th preserve of the present developed world. Moreover, agriculture in developin countries is no longer regarded as the engine of economic growth - witness th pressures on the Consultative Group on International Agricultural Research Thus it is likely that most of the world's food production would take plac in the temperate zones. Whether or not there would be the means to pay fo the food is a moot point.

One global feature is the growing divide between stable or expandin urban populations and their rural counterparts. By way of example, in the U 91.5% of the population is urban, with relatively low mobility, a birth rat per 1,000 population of half the world average, and a population doubling tim in excess of 100 years. The overall population density is high (235 person km^{-2}) revealing the extent of crowding in the urban area. No wonde misunderstanding of the rural economy is becoming so pronounced.

Conventional management of terrestrial and aquatic resources will no meet future demands. Over 90% of the world's population depend on just 1 plant and 7 animal species for food (Hillman, 1992); a tiny genetic reservoi to combat the ravages and vagaries of pests, diseases and inclement conditions. To this must be added the fact that as the only animal to coo

)d and thereby broaden the range of acceptable food species and types,)kind is faced in the arid and semi-arid regions of the developing world th a shortage of fuel for cooking.

Woody perennial species present one of the stiffest challenges for crop)agement. New initiatives are desperately needed for breeding, selection,)pagation and health of trees and shrubs.

ant Breeding

Central to the ability of the bulk of the population to move from food ltivation and harvesting to engage in social and technological advancement the provision of improved crop plants throughout the ages. Plant breeders ve always been involved in genetic engineering. Characters including yield :formance, resistance or tolerance to pests and diseases, quality mponents, uniformity and lack of prolonged dormancy periods represent the ln selection criteria. Together with advances in automation, storage and)cessing there is a complacent view that plant breeding will perpetually swer basic nutritional needs for burgeoning populations. This is acceptable.

Plant breeding programmes are protracted, expensive and are rarely lowed to proceed without interference. Basic to the needs of such)grammes is access to genetic resources for parental material. Fortunately, there has been severe attrition of genetic diversity by losses diverse wild habitats, traditional farming area, valuable collections and)lete landraces. Breeders need to screen vast numbers of clones over many ars, carry out regional trials, multiply stocks, access statutory trials and involved in marketing. Other problems faced include imprecise predictions genotype by environmental interactions, incompatibility systems between and :hin species affecting the ability to cross-breed, juvenility or ripeness-flower phases, seasonal growth patterns, changing disease virulence :terns and disease vector distributions, and complex breeding objectives volving polygenic characters. Conventional plant breeding is well-:ablished but needs to be supplemented by bioengineering technology to allow :ess to new sources of genetic variability, to speed up the process, to avel the complexities of genomes (genetic constitutions), to understand the)cesses involved in breeding, and to improve the prediction of performance products arising from the breeding programmes.

INEERING PLANTS

Modern technologies are reducing the reliance on a combination of endipity and bulk selections for plant breeding and food processing ilities.

Modern biotechnology has its beginnings with the well-known early studies deoxyribonucleic acid (DNA - actually a base!) molecules of which act as carriers of genetic information. In 1973 recombinant DNA techniques were :covered at Stanford University in California. Shortly thereafter, animal)ridomas were created in the Laboratory of Molecular Biology, Cambridge, a :covery which initiated the monoclonal antibody diagnostics industry. ing the 1980s, the inherent similarity of the genetic language in the major)ups of organisms was demonstrated by the insertion of genes or sequences :o the DNA of recipient (transgenic, genetically manipulated or modified, recombinant) organisms and sub-cellular entities containing nucleic acid.

These insertions (constructs) lead to the induction of new traits in th genetically modified organisms (GMOs).

In this period, the speciality of protein engineering came to the fore with an aim of producing customised, biologically active (eg enzymes antibodies) and structural (eg collagen) proteins for a wide range o purposes. Proteins are genetically coded amino-acid polymers with a molecula shape that helps determine function. Studies in protein engineering have bee particularly facilitated by site-directed mutagenesis of the genetic code.

Both DNA and ribonucleic acid (RNA) consist of long sequences o nucleotide bases that are attached to a backbone of alternating sugar an phosphate groups. It is the sequence of bases that constitutes the geneti code. A gene is a portion of nucleic acid that carries the code fo synthesising a specific protein or part of a protein. Each nucleic aci molecule is comprised of a linear series of genes. Between and within gene (the coding sequences or exons), though, there tend to be the so-calle introns, or intervening sequences of nucleotide bases that apparently do no code for proteins. Functional RNA molecules have the introns removed o "spliced out" by cutting out and joining (ligating) the cut ends together.

DNA acts as the blueprint whereas RNA of different types act in a wid range of functions, including the role of messenger for conveying th blueprint code to the various sites in the cell where protein synthesis take place.

Splicing and Ribozymes

Splicing is one of the key control points for cell metabolism development and differentiation generally (the "splice of life") and th mechanisms of intron recognition and splice-site selection are crucial t understanding regulated gene expression, especially in transgenic plants Certain RNA molecules have the ability to act as catalysts - the ribozymes which have led to the application of the so-called gene shears for selectivel cleaving RNA molecules without the presence of any protein; they may also b used to inactivate or destroy RNA viruses.

Antisense Technology

Gene expression in living organisms can be prevented by synthesisin relatively short RNA or DNA molecules (oligonucleotide primers or oligomers which bind specifically and selectively to complementary sequences on th target RNA or DNA molecules, switching off genes such as those controllin ethene (ethylene) biosynthesis. Both ribozymes and antisense technology ca be harnessed to combat viruses and control developmental functions in plants

DNA Fingerprinting or Profiling

When DNA is cleaved by highly specific restriction enzymes the length of the resultant fragments produce exceptionally reproducible pattern (restriction fragment length polymorphisms, RFLP) in electrophoreti separations. The patterns are inherited and can be used for diagnosti purposes. RFLPs (Bottstein et al. 1980) are used for tagging genes wit tightly linked markers for selection in plant breeding programmes. They ar also used for map-based gene cloning, assessment of genetic variability, an also for comparative genome mapping to study relationships between organisms Locating genes with respect to DNA markers on an RFLP-based map provides

arting point for cloning genes by "chromosome walking" down overlapping rge pieces of the chromosome from the RFLP tag to the gene of interest.

lymerase Chain Reaction (PCR)

A major advance has been the ability to produce simply, consistently, tomatically and cheaply, identical copies of specific DNA sequences. In sence, and there are many variants, PCR involves a series of copying cycles which double-stranded DNA fragments are firstly denatured to provide mplates for the "annealing" or binding by base pairing of two synthetic imers (short DNA molecules of known sequence that flank either side of the rget region) to complementary sequences on the DNA template strands. ereafter, the bound primers are elongated enzymically by the addition of cleotides from the reaction mixture. The resultant new DNA strands are mplementary to the template strands. One PCR cycle duplicates one DNA agment and hence produces two copies. This amplification system is employed produce adequate amounts of single or multiple genes for both fundamental d applied studies. PCR has also been used for demonstrating, mainly in imal genome mapping, high levels of polymorphism in the repeat number for mple sequence tandem repeats or microsatellites which are potentially ideal netic markers.

e DNA Approach

From the foregoing, a basic shift in philosophy has taken place in the st few decades, from the inference of the genotype from a study of phenotype rphology as was once carried out by conventional plant breeders, to a direct alysis of DNA sequence information i.e. a change in emphasis from Mendelian genomic genetics.

lectable Marker Genes

The incorporation of dominant selectable marker genes (marker genes or rkers) together with the DNA construct aids in the identification and lection of transformed cells from a background of non-transformed cells. rker genes also assist in confirming the identify of transgenic plants for gal purposes. Marker genes may encode a protein or enzyme that modifies a xic substance to render it harmless, thereby allowing the transgenic cell grow in the presence of the toxic substance. Other encoded proteins may act with compounds to produce chromogenic compounds or emit light. Yet ners enable the degradation of organic compounds, the utilisation of sugars, the conversion of heavy metal components into their metallic form. Some e even silent, producing specific, amplifiable DNA fragments e.g. lindromic sequences.

Plant pathogenic microorganisms and viruses have been a major source of A fragments for constructs which contain the marker gene. Bacterial ansfer processes (e.g. Agrobacterium, Escherichia), chemically induced gene ansfer, electroporation, liposomes, injection and particle bombardment, oibition and incubation are the most common procedures for introducing the nstructs.

In addition to normal biochemical assays, the marker gene protein or zyme can be isolated and detected by Western blotting, in which total oteins are extracted, separated and reacted with antibodies with specificity wards the gene product protein. The specific complex formed between the

antibody and the protein product can then be detected using as little as 5 10^{-9} g by a secondary reaction directed at the complexed antibody.

Molecular assays, such as Southern or DNA blotting, detect the DI sequence of the marker gene directly. Total DNA from the genetically modifi plant is digested with restriction enzymes each of which cuts the DNA in precisely defined manner. The resulting DNA fragments are separated a reacted with the DNA sequence of the marker gene that has been tagged wi radioactive or, increasingly commonly, a chemical label. Only the sequen of the marker gene will react with the labelled probe to give a complex th can easily be detected and quantified.

Where the DNA sequence of the marker gene is known from previous wor small fragments of it (oligonucleotide primers) can be synthesised. Und appropriate PCR conditions these primers when incubated with DNA from t genetically modified plant result in repeated and selective amplification c the marker gene with increases of several-million fold possible.

Concerns have been expressed about the use and safety of selectab markers in GMOs released into the environment and also incorporated foodstuffs. For example, over 30 species of plant have been modified wi genes encoding resistance for 9 different antibiotics used in human a veterinary medicine.

CONTAINMENT AND COST

Comprehensive regulations and procedures to deal with laborato activities and the containment of GMOs in UK laboratories will shortly co into force (Ratledge, 1993). To a certain extent, the Regulations redefi terms. Examples of the techniques which constitute genetic modification a as follows:

(i) recombinant DNA technique consisting of the formation of n combinations of genetic material by the insertion of nucleic acid molecule produced by whatever means outside the cell, into any virus, bacterial plasm (autonomously replicating DNA circle) or other vector system so as to all their incorporation into a host organism in which they do not occur natural but in which they are capable of continued propagation;

(ii) techniques involving the direct introduction into an organism c heritable material prepared outside the organism, including micro-injectio macro-injection and micro-encapsulation;

(iii) cell fusion (including protoplast fusion) or hybridizatic techniques where live cells with new combinations of heritable genet material are formed through the fusion of two or more cells by means c methods that do not occur naturally.

For the sake of common sense and expedience, conjugation, transduction transformation or any other natural process, polyploidy induction and in vitr fertilization do not constitute genetic modification if they do not involv the use of recombinant DNA molecules or GMOs. Likewise, the Regulations shal not apply to the following techniques of genetic modification if they do n involve the use of GMOs as recipients or parental organisms:

(i) mutagenesis;

(ii) the construction and use of somatic hybridoma cells (i.e. for th production of monoclonal antibodies);

(iii) cell fusion (including protoplast fusion) of plant cells where th resulting organisms can also be produced by traditional breeding methods;

(iv) self-cloning of non-pathogenic, naturally occurring micro-ganisms with proven histories of safe use and no known adverse consequences the environment - the so-called Group I micro-organisms where it is essary that the vectors and inserts should also be well-characterized and e from harmful sequences and should in themselves be poorly mobilizable;

(v) self-cloning and non-pathogenic, naturally occurring organisms ier than micro-organisms. Such organisms (i.e. plants and animals) must be safe in the containment facility as any recipient or parental organism.

Three levels of containment are envisaged for Group II organisms (those at do not conform to the definition of Group I microorganisms) and certain ocedures involving Group I, depending upon the evaluation of the risk sessment.

Individual scientists are legally obliged to carry out scale-dependent sk assessments of their work which will then be scrutinised and approved by ocal safety committee. The Health and Safety Executive may be involved and .l charge a fee for their services and consent. Attention will also have be paid to transport, storage and destruction of GMOs.

Historically, the UK has a superb safety record of containing and nitoring GMOs. The new Regulations may convince the public that the most ringent conditions are applied. Rather like other legal and statutory ects of health, safety and the environment, though, there is an exquisite ance to be struck between unfettered irresponsibility and high-cost straint, demotivation and export of intellectual property elsewhere. source-strapped organisations will definitely be ineligible for involvement h GMOs unless they become associated with regional centres specifically signed to meet ever-changing standards imposed by the UK or European mmunities.

LEASE OF GMOs AND THEIR PRODUCTS TO THE ENVIRONMENT AND FOR FOODSTUFFS

By and large there is relatively little opposition to using genetic ineering in most areas of health care, but as the technology is finding lication in food production, storage and processing there is widely ressed consumer concern about safety. Some GMOs and their products will tinue to be contained strictly within the laboratory environment, others .l be monitored closely over a long period to examine their suitability for ease into the environment and for consumption. A case-by-case analysis .l be carried out in every instance.

Safety is not absolute; accidents, exceptional circumstances incidents l testing occur. Anything is possible. Without resorting to examples of d transport policy, holidays in Florida, and the consequences of oxidative cesses in living organisms, the nub of the argument is one of setting the el of acceptability of risk. In this instance we are considering the risk all products arising from genetic engineering, and the risk is typically ssified according to effects on mankind.

By way of definition, hazard is a situation that may lead to harm or s; risk is the chance in quantitative terms of a defined hazard occurring.

Biologists appreciate that there is natural transfer of genes controlling formation of toxic principles in plants as well as desirable features.

For the most part, species are not static genetically. By natural selectio for example, resistances to a range of adverse xenobiotics can be develope

One huge problem is that of forecasting performance "in the field". W are not knowledgeable about selection pressures operating on organisms, n about unique recombination events likely to occur. Frankly, it is n feasible for any committee or individual to assess risk for all the possib combinations of genes. Assessment can only come from experimentation a monitoring, employing a battery of scientific disciplines. To date, releas experiments have not been problematical. Even naturally occurring mobile D elements are limited in their natural hosts, and can be regarded excessively promiscuous. In his recent article, Wilson (1993) cites that analysis of 393 defined field trials of transgenic plants (25 species) betwe 1986-1991 (in 21 countries) reveals that 50 involved "virus-resistanc traits. Field releases have shown that coat-protein-mediated protection m not behave as predicted in laboratory and growth-chamber experiment generally, there is greater susceptibility to virus challenge.

Selectable marker genes, especially relating to the potential impact c antibiotic resistance, raise questions about safety. The potential f uncontrolled gene transfer in the intestual tract, soil or by cross fertilization, or for example herbicide resistance leading to the creation c weeds have received the most attention. What little information is availab would not indicate unacceptable risk. Obviously, a great deal of research i still required to quantify risk, if any, and to make recommendations on t use of marker genes. With time, their use will in any case decline, essenti markers may need to be inactivated or eliminated prior to release c consumption of the transgenic organism.

Organisational structures to monitor GMO release are already in place i many countries. Much of the real work, though, is labour-intensive, fr removal of flowers to stop breeding of transgenics with other plant (especially weeds), surveying experimental sites to eliminate propagul (seeds tubes etc.) in the seasons following the experiment, and monitori gene flow through ecosystems. It is always a good policy for any country t monitor its vegetation anyway. I am deeply suspicious about requirements f "analysis of benefit" prior to permission being given for the release and us of GMOs. Just who sets the criteria of benefit and performs the analysis Central planning can be debilitating when prudency and responsible care a the objectives.

Genetically Engineered Foods

In the UK, the assessment of the safety of foods which are themselv GMOs or which are produced in processes involving GMOs, is a part of the rem of the Advisory Committee on Novel Foods and Processes. A decision-tr scheme has been devised to pose a series of questions which indicate the ty of information required for individual submissions to the Committee. Food c components of food derived from GMOs must be as safe as, or safer than, the traditional counterparts. The Committee is refreshingly open, as are near all scientific committees, with regard to the advice it gives to Governme and the reasoning behind that advice. Related committees include the Fo Advisory Committee, the Committee on Toxicity and the Advisory Committees c Genetic Modifications and Releases to the Environment. Their deliberatio range from food labelling to the nature of research. They function well a reinforce the confidence of the consumer that standards and proper contro are in place in a democratic environment. I very much welcome the very rece

ısible report of the Ethical Committee on Genetic Modification of Food, ıired by the Reverend Dr John Polkinhorne (1993).

ɔlic Attitudes

Voters comprise heterogeneous groups who determine the political, lustrial and economic climate of democratic countries. Their taxes and ɔse of private companies support R&D programmes in the public sector. They ɜ also consumers who should be free to exercise choice. Scientists should providing them with factual basis for reaching informed decisions.

In contrast to healthcare, applications of modern biotechnology to food l the environment are greatly influenced by the level of education, ɾceived social and ethical issues, as well as reaction, frequent irrational, ɜponses towards non-medical sciences.

There are also objections at a secondary level to the role of .tinational companies carrying out genetic engineering and failing to take ɜquately into account the impact of their activities on the less-developed ɾld or playing one economy off against another. Although not necessarily ɜociated with religious organisations, there is also the oft-cited ınatural" or "ungodliness" aspect of science replacing natural functions, ıerating chimaeric organisations, or fiddling with life for profit.

Ignorance of science and technology, as much as ignorance of business, ıds to fear, anxiety and reluctance to fund research and development ɔjects. Pressure groups of all kinds are formed. It seems that the public ɾive most of their limited understanding of science through the arts-ınated media, especially television, where all too often artistic license ɜellishes scientific observation with imaginative doom-laden claptrap. This t cause the scientific and advanced industrial communities a measure of ɾrospection. Healthy scientific scepticism, questioning, sharp debate, ɜerimentation and wide-ranging open-minded interpretations and conclusions the stuff of science. So is presentation. There can be no room for olence nor ineptitude. Scientists, like the public, cover a spectrum of ws and attitudes and are difficult to organise except into cliques. The lic must realise that it is entirely technology-dependent. Scientists in n accept justifiable control as much as the financial backing. I am ried that the foucault pendulum is swinging towards harsher controls which not be sustained in the longer term even though it is unfashionable to ue against any moves restraining science. Sometimes, pressure groups have ted political interests or social engineering at heart. Nonetheless, a ance-point must be reached, taking into account illogical fears, damage to environment, healthcare, and the need for science. The need for genetic ineering is irrefutable. It is how we do it that we must get right.

At this juncture, there is a view that only by being aware of obvious efits to the consumer (e.g. increased safety because of reduced natural ins, lower costs, post- and disease-free produce, better and more sistent quality etc.) or to the environment (e.g. reduced pesticide inputs, remediation etc.) will there be general acceptance to genetic engineering. er problems are experienced with plant-plant than with plant-microbe nsgenetics; plant-animal and animal-animal combinations, most notably where man" genes are concerned can provoke virulent public and pressure group ctions. The greatest level of acceptance will be for transgenic plants d for non-food purposes. Meanwhile, there will be a plethora of islative barriers.

CURRENT APPLICATIONS OF BIOENGINEERING

Aided by the rapid uptake of biotechnology in the higher educati sector, and relatively crude but accurate assessments of its potential decision-markers in government and private industry, genetic engineering crop plants is a world-wide phenomenon. Selective herbicide resistance to a better crop management; introduction of plant-derived insecticidal genes (e. protease inhibitors); introduction of characteristics associated wi resistance to pests, diseases, abiotic and biotic stresses; enhanced quali (e.g. amino acid composition); production of engineered oils, protein carbohydrates, enzymes etc. are examples of projects currently underway usi several crops or related species.

The diagnosis and quantification of disease organisms are increasing reliant on biotechnology, as are studies on the relationships betwe different races, pathotypes and virulence groups. To investigate the mode action and effectiveness of control agents requires the new technologies.

Plant breeding is one of the leading beneficiaries of genet engineering. All parts of normal breeding schedules are being revolutionise form describing the genetic architecture of parental material, overcomi natural breeding barriers and selections, to propagation, prediction performance and identifying more accurately the added-value properties of t progeny. Speed is of the essence, so is protection of intellectual propert

New plant varieties arising from traditional breeding methods a protected in many countries by plant variety (or breeder's) rights (PVR without recourse to patent law. Patents are now being granted for t protection of recombinant methods for the production of transgenic plants a their resultant products. Attempts are being made to harmonise patent law a practice internationally. Ethical concerns are expressed about patenti life-forms and claiming ownership. There is freedom to research under bo patent and PVR law, but freedom to commercialise is complex, and therefo plant breeders using modern technologies seek protection of both types f law.

Patent protection is unlikely to affect access to existing germplasm a traditional varieties. Genetic resources and diversity are internationall seen as the common heritage of humankind. Biotechnology adds to genet diversity. Counterarguments centre on the farmer's privilege to save seed produce subsequent crops without royalty payments to recoup R&D costs, abu of monopoly provisions, "ordre public" and the public interest, and also t nature of more discovery. Unfortunately for all concerned, a patent invention does not guarantee a reward for the inventor; simply put, it giv an opportunity for the inventor or patent proprietor to profit from t invention where there is a profitable market for it. Secrecy in some cas is the best commercial protectant in the short term.

For transgenic plants to achieve a small portion of their potentia basic studies will need to expand on the factors (e.g. promoters etc regulating the expression of introduced genes in different organs and tissu at various phases of growth and differentiation. Industry would be assist by studies on the biosynthesis and degradation of complex natural polyme such as lignin, cutin, suboin and cellulose, manifestations of ce differentiation, and the cellular components of industrial relevance. Sing gene studies will give way to polygenic linked constructions.

Bioremediation could have a highly publicity profile for genetic ineering to assist in measures to reverse environmental degradation. Most rent research is initially concerned with the construction of roorganisms that can degrade, on command, oil and organic xenobiotics such polychlorinated biphenyls. Future research is likely to include the duction of transgenic plants that can withstand abiotic "stresses" such as h salinity, heavy metal and radionuclide contamination, sewage and factory luents.

Dinomania apart, the retrieval of nucleic acids from fossils and served tissues is of merit for evolutionary studies of all kinds, and for earch on adaptation to climates, predation and disease.

tection of Crop Plants - The Virus Example

Crop protection deserves conferences of its own. A daunting matrix of ts and diseases, vector systems, host types, mechanisms of infection and estation, control measures, economics, impact assessments, and variability fronts every reviewer. Biotechnology finds its greatest sophistication in p protection in the area of virology, for understandable reasons connected viral *modus operandi*.

Most plant species are naturally resistant to the majority of the 675 or e plant viruses currently identified. All crops, however, are prone to nificant yield and quality losses caused by one or more viruses. Plant al genomes are plastic and resistance-breaking virus strains are rapidly duced in monocultural agricultural systems with intense selection ssures. This, in turn, causes difficulties for plant breeders attempting introduce dominant and durable resistance genes: there may be true unity, subliminal infection or symptomless tolerance to infection. No istance genes *per se* have been characterised to date. For many years, re have been observations that infection with mild, symptomless or enuated strains of viruses could "cross-protect" a range of field crops inst closely related, but severely pathogenic virus strains. Virus-istant crops have been created in many countries by genetically engineering n to express part of a viral genomic or virus-associated sequence. Cognate jects on virus control measures are aimed at the virus vectors (nematodes, ects and fungi) and the molecular features determining virus transmission replication.

Transgenic plants expressing viral-derived sequences have been discussed sites for hyper-evolution of pathogenic viruses through recombination nts. There is no supporting evidence for this. Any long-term genetic or demiological effects would seem remote.

An exciting concept for future work is the protection against fungal, erial and viral diseases by expressing appropriate antibodies in nsgenic plants. Eventually, we would like to be in a position to solve istance gene construction and action.

CLUSION

Genetic engineering is here to stay. No doubt the introduction of the el was foreseen by some to require road traffic legislation as a way to ay development. The technology is clever and takes science and industry

into a new phase of opportunity. Our shared responsibility is to get i right.

ACKNOWLEDGEMENTS

I thank my colleagues J.W.S. Brown, K. Harding, W. Powell and T.M.A Wilson for helpful discussions. SCRI is grant-aided by the Scottish Offic Agriculture and Fisheries Department.

REFERENCES

Botstein, D.; White, R.L.; Skolnick, M.; Davis, R.W. (1980) Construction of a genetic linkage map in man using restriction fragment lengt polymorphisms. American Journal of Human Genetics (32), 314-31.

Carruthers, I.D. (1993) Going, going, gone! Tropical agriculture as we kn it. The Tropical Agriculture Association Newsletter, 13/3, 1-5.

Hillman, J.R. (1992) Opportunities and problems in plant biotechnology - a overview. Proceedings of the Royal Society of Edinburgh, (99B)(3/4) 173-182.

Ratledge, C. (1993) Containing genetically modified organisms. Biologis (40)(2), 78-79.

Report of the Committee on the Ethics of Genetic Modification and Food Use. 1993. HMSO ISBN 0 11 242954 B.

Wilson, T.M.A. (1993) Strategies to protect crop plants against viruses: pathogen-derived resistance blossoms. Proceedings of the Nationa Academy of Sciences, USA, (90), 3134-3141.

FURTHER READING

Da Silva, E.J.; Ratledge, C.; Sasson, A. (Eds.) (1992) Biotechnology. Economic and social aspects. Cambridge. Cambridge University Press.

Flavell, R.B. (1991) Molecular biology and genetic conservation programmes Biological Journal of the Linnean Society (43), 73-80.

Grierson, D. (Ed.) (1991) Plant biotechnology Vol. 1. Plant genetic engineering. Glasgow. Blackie and Son.

Persely, G.J. (Ed.) (1990) Agricultural biotechnology opportunities for international development. Allingford. CAB International.

Powell, W.; Hillman, J.R. (Eds.) (1992) Opportunities and problems in plant biotechnology. Proceedings of the Royal Society of Edinburgh, 9 (3/4).

NOTES