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BIOTECHNOLOGY
PAST, PRESENT AND POTENTIAL

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BIOTECHNOLOGY: ANCIENT AND MODERN

Louis Pasteur wrote "There are no applied sciences; there are only applications of science...The study of the application of science is very easy to anyone who is master of the theory". A few years later Lord Kelvin instructed us that "If you can measure that of which you speak, and can express it by a number, you know something of your subject. But if you cannot measure it, your knowledge is meagre and unsatisfactory." It would indeed be interesting to know what the spirits of these distinguished scientists are thinking about "Biotechnology" which takes within its broad embrace remarkable new knowledge in cell and molecular biology; some very ancient technologies; together with a large swatch of empirical observations and discoveries, many of which remain far distant from viable technological application.

Fermentation technologies have a very long history: beer, wine, bread and cheese having been around as long as cereals and vine fruits have been harvested and animals have been milked. Homer described wine as a gift from the Gods and Ecclesiasticus wisely advised that "From the beginning wine was created to make men joyful, not to make them drunk."

Though ethanolic fermentations have been most pervasive, lactic and other acidic fermentations have appeared in greater diversity, particularly in traditional domestic processes of preservation. The ancient Sumerians 7,000 years ago converted all their milk into cheese in the stated belief that had God intended mankind to have clean milk to drink he would have placed the udders at the front end of the cow.

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In addition to the hundreds of cheese varieties, buttermilk, sour milk and yogurt, with which all Americans and Europeans are familiar, other lactic milk products include kefir, koumiss and vilia in the Slavic and Scandinavian countries. Egyptian kishk, Greek trahana, Indian idli, Nigerian ogi, Kenyan ugi and South African majou are but a few of many lactic-cereal ferments. Lactic vegetable pickles have been eaten in the Middle East and throughout much of Asia for as long as we have historical record. Lactic acid as such has been manufactured in the United States for more than 100 years.

Acid fermentation of milk, vegetables, fish and meat are among the most widely applied and trusted methods of preservation in many Asian tropical countries. Though the lowering of pH to levels at which pathogens will not grow and the generation of hydrogen peroxide and the antibiotic nisin by Lacto bacilli are well-known to food technologists, the systematic industrialization of traditional fermentation industries in Asia has been less extensive than might have been expected. Perhaps the revived interest in biotechnology and fermentation systems will serve to change this situation in the future.

Though some would have us believe to the contrary, the word "Biotechnology" is far from new. A Bureau of Biotechnology existed in Leeds over half a century ago, the first copy of the Bulletin of the Bureau of Biotechnology being published in July 1920. This Bureau metamorphosed out of a consulting practice which was publishing papers on brewing and other fermentation technologies as early as 1899. The Leeds consultant laboratory was among the first to provide industrial consultant services in both chemistry and microbiology.

UMIST and its related institution along Oxford Street have distinguished records in fermentation biochemistry. Dr. Thomas Kennedy Walker welcomed the first students to his new Department of Fermentation Industries in this Institution in 1923. Walker later changed the name of the department to "Industrial Biochemistry", which semantically seems little different from "Biotechnology". The imaginative pioneering contribution which Professor Walker made to the foundation of food science and the training of so many of

its early practioners in Britain has never been adequately recognized. His former students are to be found in biological research institutions and industries not only in Britain but throughout a great many developing countries.

During his life in Manchester, T.K. Walker and his graduate students published more than 170 papers covering a fascinating range of applied microbiology and fermentation technologies. In light of the renaissance of industrial microbiology within the family of contemporary biotechnologies, Walker's pioneering work deserves to be revisited by present day practioners. One of Professor Walker's distinguished colleagues was Dr. James Mounfield, the founding father of the IFST who made many important contributions to our knowledge of panary fermentation.

In 1909 in Manchester University, to which he had moved from Geneva in 1904, Chaim Weizmann, working under Perkin, began his search for a bacterial strain that would convert carbohydrate to iso-amyl alcohol, a precursor via isoprene of synthetic rubber. Instead, in 1912, he isolated the strain of Clostridium acetobutylicum which converts carbohydrate into butanol, acetone and ethanol in the ratio of 6:3:1. The process was extensively used to produce the acetone needed by the military to plasticize cordite during the First World War. Following WWI butanol gained wide acceptance in lacquers for automobiles. Weizmann's acetone-butanol process and Walker's elucidation of the role of the polyphenolic antiseptics, lupulone and humulone, are of contemporary importance to the organic chemical and brewing industries respectively.

Elsewhere I have attempted a more comprehensive review of the state of the biotechnological art (IDRC, 1985) and of the history of biotechnology in the food industries (Hulse, 1984; Hulse, 1985). The scope of this presentation will permit little more than a superficial overview of some of the more interesting developments as they relate to agriculture, food, human and animal health. In conclusion I shall attempt to address what I see as some

important implications for humanity in general together with some particular issues of concern to academic institutions, industrial organizations and developing countries.

CONTEMPORARY BIOTECHNOLOGY

The more enthusiastic advocates of biotechnology would have us believe that the potential applications of rDNA techniques for human benefit are limited only by the imaginations of those who seek to manipulate and apply them to industrial and commercial use. Nevertheless, experience suggests, particularly in the medical field, that hoped for benefits may well be more elusive than originally anticipated.

The uncertainties attendant upon the new biotechnologies are such that future market prospects cannot be reliably forecast by econometric or other predictive methods. In spite of the immense interest aroused by the remarkable, and for the most part favorable, publicity the subject has received, with the possible exception of Japan few nations seem to have established well-defined and coordinated programs for bioscientific research and biotechnological development.

Though, theoretically, a biotechnology could be elaborated for any industrial process in which a biological catalyst or process of transformation can replace one based on chemistry, greatest investment and probably most progress will be in the biomedical field, in large part because pharmaceutical products carry a high value added and can be arbitrarily priced to recover the cost incurred in research, development, manufacture and distribution. In spite of George Bernard Shaw's warning to the contrary, most of us would like to live forever and there seems almost no limit to what wealthier nations will pay to protect their health and to lengthen their lifespan. Thus the cost of a biotechnology congenial to a pharmaceutical manufacturer could quickly bankrupt a food processor.

It now seems acceptable to separate the subject into (a) the old and traditional and (b) the new or contemporary biotechnologies. If for convenience we accept this categorization, the following is a chronological calendar of contemporary biotechnology.

1953 the twin helix of DNA was described.

1973 the first gene was cloned.

1974 a cloned gene was first expressed in a different bacterial species.

1975 the first hybridoma was created. Also at the Asilomar Conference, the U.S. formulated its first safety guidelines for rDNA research.

1976 GENENTECH was the first U.S. company founded to explore and exploit rDNA research.

1976 the U.K. Government established the Genetic Manipulation Advisory Group (GMAG).

1980 the U.S. Supreme Court ruled that microorganisms could be patented under existing law.

1980 GENENTECH's first public stock offering recorded the fastest price per share increase on record. The price rose from $35.00 to $89.00 per share in 20 minutes.

1981 CETUS established a Wall Street record by raising US$115 M in its initial public stock offering.

END OF

1981 more than 80 new biotechnology companies had been formed in the U.S.A.

1982 the first rDNA animal vaccine for colibacillosis was approved for use in Europe and the first rDNA pharmaceutical (human insulin) approved for use in the U.S. and the U.K.

The vast array of new industrial processes forecast by the more ardent advocates of modern biotechnology are fascinating indeed. One is reminded of the enthusiasm for nuclear fission 25 years ago promising irradiation technologies to generate an infinite variety of new plant mutants; total sterilization and disinfestation of perishable foods; a limitless supply of energy independent of fossil fuels. Once again scientific imagination may have to be tempered by economic pragmatism.

It is conceivable that a variety of microorganisms and plant cells could be genetically engineered to generate new organic compounds as starting materials for further chemical synthesis. Outside of the pharmaceutical and fine chemical fields such does not seem to be imminent, probably because of the high cost of research and scale-up compared with established industrial organic chemical synthetic processes.

FOOD & DRUGS

While in legislative protocols food and drugs usually walk hand in hand, biotechnology in food processing long predates its establishment in pharmaceutical industries. Nevertheless in contemporary biolotechnology, levels of investment in food and pharmaceutical research are of very different orders of magnitude. Roughly 75% of U.S. Government investment in biotechnology research is directly related to the health sciences. The largest multinational pharmaceutical companies invest more than 12% of their sales income in research. Hoffmann-Laroche reputedly invests 13.8%. In comparison food industries in Canada invest less than 0.2% of sales on research. The total world value of pharmaceuticals and related health chemicals is estimated close to US$100 B of which the U.S. consumes about 10%.

Close to 20% of all drugs are derived wholly or partially from microorganisms, antibiotics being the largest single class of microbiologically derived drugs. Alexander Fleming's discovery in 1928 that Penicillium notatum destroyed cultures of Staphylococcus aureus led to the eventual isolation by Florey of penicillin. About 300 new antibiotics are reported every year, most being isolated from Streptomyces species of Actinomycetes.

Over the past quarter century fermentor yields of penicillin have increased from a few milligrams to over 20 g/l. These increased yields have resulted from the selection of superior strains among random mutants together with significant improvements in fermentor design and operation. In the foreseeable future further improvements in antibiotic production will more likely result from established industrial microbiological procedures than from genetic engineering. Syntheses of primary proteins are largely controlled by single genes, whereas antibiotics and other secondary metabolites require expression of up to 30 genes. Nevertheless, some progress has been reported in generating new and modified antibiotics through protoplast fusion of different Streptomyces species.

The large pharmaceutical companies require between 8 and 10 years and up to US$100 M of investment to bring each new drug to the market. The larger U.S. companies employ sales forces of 500 or more to convince medical and pharmaceutical professionals of the merits of their products. Despite these large R&D commitments fewer new drug introductions appear now than in former years. The contributing constraints include: more rigorous government legislation; relatively short periods or inadequacy of patent protection for new drugs; competition from generic and "no-name" products sold at lower cost than the established name brands. Though biotechnology seems unlikely in the near term to reduce the high costs of marketing and distribution, new techniques will probably reduce research and development time for biological screening, pharmacological testing and clinical evaluation.

Pharamcological effectiveness requires the precise correlation of physiological function with molecular structure. Accurate determination of the structure of drug receptor molecules in living organisms by gene cloning and DNA sequencing research will likely define the biochemical structure of new drugs that will react effectively with identified receptors. The integration of computers with these novel and elegant techniques offers a more expeditious means of arriving at chemical structures which provide the potency and effectiveness desired. The potential spinoff for nutritional and food biochemistry, though not immediately evident, is nonetheless a distinct possibility.

If novel biotechnological techniques can reduce the cost of research and development substantially, the pharmaceutical industries may be more disposed in the future than in the past to address some of the serious tropical infectious diseases that debilitate millions of people in developing countries. There is, however, the danger that drugs and other biological materials may be released into countries where protocols and regulatory mechanisms for ensuring safety do not exist or are not rigorously applied. The International Organization of Consumers Unions (IOCU) has repeatedly drawn attention to the sale in developing countries of drugs that are restricted or banned in the more advanced nations in which they are manufactured. The IOCU reports that anabolic steroids and other dangerous drugs may be bought without medical prescription across the counter in many developing countries.

ANIMAL PRODUCTION

Of particular interest to food and agricultural scientists are the various hormones that regulate reproductive physiology and rates of growth. The value of animal growth hormones is estimated at US$500 M annually, half of which are used in the United States. Throughout the world the employment of animal growth hormones is increasing at a compound annual growth rate of 25%. GENENTECH, in cooperation with Monsanto, are producing a variety of animal growth hormones by rDNA techniques. In addition, growth hormone research is examining the complex nature of growth development and animal productivity.

Injections of purified growth hormones can increase milk production by up to 17% without change in feed intake. Sheep and hogs show rapid growth and improved feed conversion efficiency following GH treatment. However, the long-term effects of GH administration on the health of animals to which they are administered and upon consumers is causing growing concern. Of particular concern to food technologists is the influence of GH treatment upon carcass quality.

Various microbially derived products are being examined to improve feed efficiency: some destroy or inhibit bacterial, protozoal or other parasitic organisms in the GI tract; others stimulate the growth of beneficial microorganisms in the gut. The possibility that rDNA-derived, highly resistant pathogenic organisms spread from animal faeces may present a serious public health hazard is not to be treated lightly. Consequently, more research and reliable control protocols are required before products that significantly alter intestinal flora can be permitted for widespread use.

Following the widely publicized transfer of rat growth hormones into mice and because the injection of growth hormones derived from industrial fermentations may carry with them unwanted pathogens, research is in progress to insert growth hormone genes into animal genomes.

The high cost of deep-sea fishing caused by escalating prices of transportation fuels has stimulated investment in fish culture. Commercial fish culture requires, first, the production of gametes from brood stock, followed by the rearing of the resultant offspring to healthy fish of marketable size. Selective breeding for more efficient feed conversion requires several generations and many years of research, and the time taken to reach economic size and weight is, for many species, uneconomic.

Scientists in Canada report that inoculation with the natural growth hormone extracted from the pituitaries of bovines and poultry significantly increases specific growth rate and feed conversion in Cohoe salmon. The genes that regulate the production of growth hormones in both poultry and bovines have

been transferred by a plasmid vector into E. coli. Satisfactory expression of the cloned genes results in the microbial generation of biologically active recombinant growth hormones which, it is anticipated, will be satisfactorily used to increase the rate of growth of both juveniles and adult Salmonids thus reducing the time and cost of production.

Of equal interest is the hormonal control of reproductive systems in both terrestrial and aquatic animals of economic importance. Research supported by IDRC in several Asian countries has demonstrated how gonadotropins extracted from the pituitaries of Pacific salmon and Asian carp can induce gravid female fish to lay their eggs which they are often reluctant to do when held in captivity.

Hormone-induced super-ovulation in domestic cattle is gaining increased recognition in animal production systems. The hormone is impregnated onto a vaginal tampon. Super-ovulation by growth hormones may trigger the release of between 10 and 20 eggs per year, making possible large numbers of genetically superior offspring from elite cows. These embryos can be twinned to produce identical individual calves. In practice, one embryo can be implanted in a surrogate mother cow, the twin embryo being frozen until the implanted embryo demonstrates the viability and superiority expected of it. In many instances, a transplanted embryo carries with it the immunities from its genetic origin and then acquires the environmental immunities from its surrogate mother.

The International Laboratory for Research on Animal Diseases (ILRAD, 1985) is working to reduce the incidence of trypanosomiasis, a protozoal disease which induces severe morbidity and mortality among cattle over an area of Africa equal to that of the United States. The N'Dama cattle in Gambia show significantly greater resistance to trypanosomiasis than many other breeds. ILRAD has induced ovulation in N'Dama cows, transported the embryos in the frozen state before implantation in Kenya into trypanosome-susceptible Boran cows. The cryogenic techniques available permit the preservation of up to 100 embryos which can be stored and transported in a container no larger than a suitcase.

Some observers suggest that genetically derived vaccines for animals offer greater potential profit to manufacturers than those for humans. It is argued that to acquire immunization, human beings require relatively few and infrequent doses of potent vaccines. In contrast, farm animals are continuously slaughtered and therefore each new animal needs individual immunization. It has also been suggested that safety requirements for animal vaccines are less exacting and therefore the cost of bringing them to market is lower than for human vaccines.

Though this argument is of dubious validity, given the high price that wealthy nations will pay for pharmaceuticals that may control cancer and other fatal maladies, research is in progress to produce vaccines for various animal diseases among which Foot-and-Mouth Disease ranks high in importance. More than 800 M doses of attenuated FMD virus vaccine worth over US$250 M are administered annually. The FMD vaccines available vary considerably in their effectiveness against different viral strains. GENENTECH, in collaboration with the U.S. Department of Agriculture, claims to have cloned into a bacterium the DNA that encodes the protein for one important strain of FMD. The vaccine has been produced in sufficient quantities for field trials to determine how broad is its spectrum of effectiveness.

If the generation of rDNA derived vaccines for viral diseases appears difficult, those for bacterial and protozoal infections are infinitely more so. The protozoa which cause trypanosomiasis carry their antigens as glycoproteins on their surface coatings. Each antibody developed by the animal's immune system acts to neutralize a specific trypanosome antigen. At least 100 genes are at work continuously modifying the chemical structure of the antigens. The animal's defensive mechanism is thus rarely able to keep up with the continuous change in antigen structure. Consequently, the hope for vaccines that will confer permanent immunity against protozoal diseases appears remote in the near future.

ANALYTICAL AND DIAGNOSTIC TOOLS

Recombinant DNA technology is however providing important diagnostic tools both for human and animal diseases. The production and application of murine monoclonal antibodies has been sufficiently well publicized to need no description. An equally important diagnostic tool is DNA hybridization which occurs when two separate single strands of DNA join to reform the double helix. The two strands must have exact corresponding sequences of nucleotide bases for hybridization to occur. A given strand can hybridize only with its complementary strand. Radioactive phosphorus is being incorporated into the DNA strand known as the "probe". Hybridization, when it occurs, can be followed by the radioactive label.

DNA hybridization probes can be used to identify and isolate particular DNA sequences and to determine where certain DNA sequences are located on particular chromosomes. A probe-DNA isolated from a pathogenic virus can be used to identify that virus within plant or animal cells thus making possible specific diagnosis. DNA hybridization probes offer more precise methods of diagnosing infections and of identifying specific DNA sequences in naturally occurring and synthesized biological materials.

PLANT CELL AND TISSUE CULTURE

It is 125 years since Gregor Mendel uncovered the patterns of inheritance displayed in the progeny of genetically different plant parents. Mendel's elucidation of how characters are combined and inherited provided the basis for all subsequent plant and animal breeding.

Conventional plant breeding proceeds through collection, classification, selection, combination, recombination and propagation. Germplasm collection seeks to bring together a smorgasbord of genotypes, embodying a broad range of identifiable and inheritable characters. From these are selected plants which display desirable characters. Where all the characters desired are not found

in a single genotype, sexual cross-breeding seeks to combine the desirable characters from different parents. Desirable characters not found in the germplasm bank may be introduced by accessioning wild relatives or by induced mutation. Unfortunately, mutation induced by irradiation or chemical mutagens is quite unpredictable and uncontrollable.

The ultimate plant breeding objective is to generate pure lines: cultivars that are genetically stable and homozygous, having inherited identical chromosomes from both parents. To achieve homozygosity so that a plant carrying a combination of desired characters will breed true, requires that the cultivar be "selfed": that it be fertilized with its own pollen through five or six succeeding generations. This long and tedious procedure explains why it takes 8 to 15 years to develop new cereal varieties to the stage at which they can reliably be licensed. Once a homozygous pure breeding line has been realized its seed must be multiplied into quantities sufficient for commercial distribution, another time-consuming procedure.

Plant cell and tissue culture provide means of short circuiting and reducing the time required for many of these conventional processes, in addition to providing the basis for a new generation of industrial biological technologies.

Cell culture is based upon totipotency: the biological phenomenon whereby every somatic, non-sexual cell embodies a twin pair of chromosomes each carrying all the several million genes the plant needs for systematic growth, metabolism and other essential functions. Theoretically, every somatic cell is capable of producing a whole new plant if appropriately cultured. If this were invariably so, one cm^3 of vegetative tissue could generate about one million identical plant clones. In fact, at best, relatively few cells will yield new viable plants when cultured.

Plant cells, like microorganisms, can be cultured in nutrient broth or solid media. The processes are as yet empirical and, according to the source of the tissue cells, the composition of the medium, and the ambient conditions

the cells may proliferate into a callus: a mass of undifferentiated cells; or into an organized differentiated pattern so arranged as to form a small plant with a shoot and a root. In some instances, progressive sub-cultures of primary callus in differing concentrations of the plant growth hormones, auxins and cytokinins will stimulate successively the emergence of a shoot and a root. The advantages of tissue culture include:

(1) propagation of large numbers of plants from a single superior parent;
(2) generation of disease-free plants from infected parents;
(3) generation of plants difficult to propagate sexually.

The time-consuming process of generating pure in-bred lines has been described. Every sexual cell, whether from pollen or ovaries, contains a single set of chromosomes. Consequently, plants propagated from pollen or anthers will be sterile and incapable of reproducing themselves. By treatment of the anther culture with colchicine, an alkaloid extracted from the autumn crocus, each single chromosome will double, the second chromosome being identical to the first. In this way homozygous pure breeding lines can be generated, eliminating many years of self-pollination.

Canadian plant breeders are employing pollen culture to produce superior elite lines of rapeseed, combining high yield potential with lower erucic acid and glucosinolate contents. The technique offers the early realization of superior lines of several tropical legume crops. It is also reported that anther culture has produced viable, genetically stable, homozygous pure lines of barley, rice, rye and wheat.

Oil palm is a naturally outbreeding species. Consequently, the breeding stock carries a high incidence of heterozygosity and progeny display significant variance in identifiable genetically controlled characters. Tissue culture offers promise to oil palm breeders of being able to select individual plants each with a desirable combination of characters. The techniques of culturing oil palm are complex and need not be described.

Propagation by tissue culture offers the hope of combining high yields of palm oil together with a desirable fatty acid composition (Jones, 1983; Jones, 1984).

SOMACLONAL VARIATION

At first it was assumed that all plants regenerated from the same parent plant by tissue culture would be identical clones. Such is by no means always the case. Plants arising from cell or tissue culture may possess markedly different characters, each from one another and from the parent plant from which the tissue was derived. It appears that while progressing from the original organized differentiated state in the parent plant, through the disorganized undifferentiated callus, then back to a newly organized differentiated state in the form of new plants, the chromosomes break up and the genetic code is reassembled in different sequences in each new plant.

Being derived from somatic tissue these progeny, genetically different from the parent cells, are described as somaclonal variants. Though uncontrollable and unpredictable they may offer a significant new source of genetic variability for plant breeders. In addition they may provide novel starting materials for the manufacture of new biologicals of economic value.

NITROGEN FIXATION

It is a popular misconception among journalists that rDNA techniques now make possible the transfer from legumes to cereals of the genes which control symbiotic nitrogen fixation in the root nodules. Unfortunately, in legumes at least 17 genes (*nif* genes) are involved in the process of biosynthesizing protein from atmospheric nitrogen. The reduction of atmospheric nitrogen to ammonia in a living leguminous plant or in a chemical p ant by the Haber Bosch or Cyanamid process absorbs large inputs of energy. The reduction of between 12 and 15 moles of ATP is needed to provide the energy to reduce one mole of nitrogen in a legume nodule. The Haber Bosch process requires a pressure of 1,000 atmospheres and temperatures of close to 600°C; the temperature of the

Cyanamid process is even higher. Even if the genes could be transferred, sequenced and induced to express themselves in a cereal grain, the energy used could very well show up in a significant reduction in total biomass yield. Also, unless the biochemical pathways in the cereal were appropriately modified, the increased nitrogen might deposit itself elsewhere than in the seed.

Much greater hope lies in the genetic manipulation of such nitrogen fixing bacteria as Rhizobia which cause nodules to form in legume roots where they convert atmospheric nitrogen to ammonia which the plant synthesizes into protein. Some success is also reported in the genetic manipulation of free living nitrogen-fixing soil bacteria by improving their association with the roots of cereal plants.

The most widespread of the free living nitrogen-fixing organisms are the blue-green algae, some species being adapted to terrestial, others to aquatic conditions. Some survive in the Antarctic at near freezing temperatures, others above 60°C in hot springs. The association between Anabaena azolla and the aquatic fern Azolla pinnata in tropical aquatic environments reportedly produces up to 150 km of nitrogen per hectare per year. The azolla is used to fertilize rice paddies or as forage for ducks and pigs. Naturally occurring heterotrophic nitrogen-fixing bacteria and blue-green algae can fix up to 50 kg N/ha in submerged rice paddies that receive no nitrogen fertilizer.

PROTOPLAST FUSION

Bacterial DNA contains about 5,000 genes; a plant genome may contain anywhere up to 50 M genes of which less than 5% are actively synthesizing protein at any one time. Consequently, the genetic manipulation of higher plants is much more difficult than the transfer of expressive genes into the DNA of bacteria. However, as already stated, cells excised from any part of the plant: leaves, stems, roots, flowers, pollen, or buds, may be induced to propagate when dispersed and suspended in an appropriate nutrient medium.

Propagation is also possible from protoplasts: plant cells from which the cell walls have been removed mechanically or biochemically. Protoplasts may be subjected to experimental manipulations virtually impossible with intact cells. For example, protoplasts can take up foreign genes by microinjection. Protoplasts from different plants may be fused to produce hybrids unattainable by sexual crossing. Nevertheless, so far it has proved difficult in many species to regenerate whole healthy plants from protoplasts. Also, where whole plants have been derived from the hybridization of widely different genera, many have proven sterile and unable to reproduce themselves.

In addition to propagating plants from somatic vegetative tissue, cell fusion and tissue culture offer means of manufacturing secondary metabolites to be applied as insecticides, pharmaceuticals, fragrances, flavours and various other substances useful to food, pharmaceutical and other biological industries.

PLANT METABOLITES

The plant breeder requires that tissue culture generate a shoot and a root. Plant metabolites of economic value may well be produced from undifferentiated cell cultures, only those cells which synthesize the metabolite being propagated. At present the industrial production of plant metabolites is constrained by a somewhat primitive state of the art and the high cost of production. It has been estimated that the end product must demand a price of at least $600/kg if production by tissue culture is to be economically feasible. Shikonin, an ingredient of cosmetics, is reportedly manufactured by the culture of Lithospermum cells in Japan. Other substances now extracted from wild or cultivated plants that are being considered for production by tissue culture include codeine, opium, jasmine, digitoxin, quinine and reserpine.

Theoretically, any plant metabolite can be manufactured by cell culture, the advantage being the relative freedom from the hazards of weather, parasites, pests and diseases to which the growing plant is always susceptible. It is evident however that large-scale factory production of important tropical plant derivatives by cell culture could have serious consequences for many developing countries. The adverse effect of high fructose corn syrup (HFCS) upon cane sugar production is indicative of the serious incursions upon tropical agriculture that similar biotechnologies might bring about in the future.

Certain bacteria induce tumors in plants by inserting their bacterial DNA into the plant's chromosome by means of a vector called a tumor-inducing (Ti) plasmid. This knowledge has been applied to introduce into Ti plasmids genes which can then be transferred into a plant's genome.

It is reported that a gene which conveys resistance to an extremely potent herbicide has been transferred in an expressive form into cereal grains. It is important to emphasize that the goal of this biotechnological exercise is not to provide a plant needing less herbicide but rather to proliferate plants that tolerate increased herbicide use and therefore stimulate a greater demand for the purchase and application of herbicides. It is not surprising that large manufacturers of herbicides and other agricultural chemicals are acquiring control of major seed companies.

The difficulty of scaling-up from a laboratory flask to a large batch fermentor is familiar to anyone who has worked in a brewing, pharmaceutical or other fermentation industry. The rapidly growing interest in plant and microbial cell culture has therefore led to extensive investment in continuous processes that employ immobilized cells or enzymes.

IMMOBILIZED CELLS AND ENZYMES

Naturally occurring biochemical conversions by immobilized organisms are widely evident, particularly in oceans, lakes and other aquatic environments where bacteria, molluscs, micro and macro algae attach themselves to solid surfaces and metabolise nutrients absorbed from the passing currents. Of particular economic importance are such mollusc filter-feeds as oysters, clams and mussels which are motile only during their early stages of life. Attached to rocks or mangrove roots in the wild, or to rafts, racks or ropes in artificial culture, the molluscs filter their essential nutrients from the water which passes through them.

Hundreds of carriers, attachments and reaction mechanisms are being examined in immobilizing living cells and enzymes for continuous biochemical conversions. The techniques can be crudely classified as (1) adsorption; (2) covalent attachment; and (3) entrapment. Combined systems may, for example, use covalent linking to strengthen weakly adsorbed or gel-entrapped materials.

Quick vinegar - the conversion of ethanol into acetic acid by passing wine over wood chips carrying aceto-bacter - is one of the oldest examples of immobilization by adsorption. In 1916 invertase was successfully adsorbed onto charcoal and aluminum hydroxide to hydrolyze sucrose. Among the earliest industrial applications, immobilized amino-acylase from Aspergillus oryzae adsorbed onto a DEAE-Sephadex column was used to separate the L- and D-optical isomers from racemic mixtures of the chemically synthesized amino acid.

Adsorption relies upon attachment by such reversible bonds as electrostatic attachments and Van der Waal's forces. The many adsorption carriers reported include clays, sand, diatomaceous earths, glass, mineral salts, metallic oxides, ceramics and various organic polymers. The unpredictability is illustrated by the highly variable behavior of lactase when immobilized into silica (SiO_2), and titanium oxide respectively. On silica the enzyme activity was significantly higher at pH 3 than at pH 7. On

titanium oxide the reverse was the case. At both pH levels enzyme activity was 3 to 4 times greater on titanium oxide than on silica. The average pore size of both carriers (ca. 370 Angstroms) was roughly the same.

In spite of the research attention it has been given, immobilization by covalent cross-linking has gained relatively little commercial application. Reagents are generally expensive and those that are toxic to living cells are inadmissible for food, beverage and pharmaceutical processes. In many instances it is either not technically feasible or too expensive to regenerate the carrier. Nevertheless, the immense range of options among possible covalent attachments offers exciting possibilities for the future of immobilized catalysts. If ever the alternatives can be reliably and systematically brought together, a computerized decision tree would be a valuable aid to making reliable choices among them.

Immobilization by entrapment depends upon the occlusion of an enzyme or cell within a hydrophobic gel, a polymer, a membrane or a fibre. Such systems accept only substrates and reaction-products relatively small in particle size. Materials reported upon include polyacrylamide gels, polyurethane foams, silastic and starch gels, acrylic resins and collagen. Entrapment is achieved by gelatinization, polymerization or coagulation of a solution or dispersion of the cell or enzyme in an aqueous medium. In fibre entrapment, the solution is extruded through a spinneret into a coagulant bath, similar in principle to processes used to manufacture nylon and texturized vegetable protein.

Entrapment is attractive in that the catalyst exists in dispersed aqueous droplets. There being no chemical bonding, the integrity and stability of the cells and enzymes are relatively well preserved. On the other hand, control of pore size is critical and difficult. Pores that are too large permit leakage of the catalyst; pores that are too small or cells that are too densely packed will inhibit diffusion of the substrate solution and restrict reaction to the surface areas.

An attractive but relatively little exploited opportunity is to imprison living, actively metabolizing microorganisms in a porous matrix. Even mild toxicity of the medium of entrapment may not be an absolute constraint. For example, in the production of aspartic and malic acids, enzyme catalysis continues following mortality of the bacteria entrapped in polyacrylamide.

Most widely publicized is the manufacture of High Fructose Corn Syrup, total annual production of which exceeds 3 M tonnes. In North America, HFCS has replaced more than 36% of the sucrose formerly used in industrial manufacturing. Though the conversion of glucose by immobilized glucose-isomerase is industrially well established, research to identify superior enzyme sources and more efficient continuous reaction systems is still in progress in several countries.

In contrast, there seems little likelihood that the well established batch conversion of corn starch to glucose syrup, derived from the wet milling of maize, will give way to a continuous process employing immobilized alpha-amalyse and gluco-amylase. Both enzymes suffer impaired efficiency when immobilized and, despite the theoretically shorter conversion time in a continuous process, and the many attempts at adsorption, covalent attachment and entrapment, the batch process remains commercially undisturbed. Thus, the manufacture of HFCS from corn starch will continue as a combined batch plus continuous process.

Research efforts to immobilize lactase for the conversion of lactose in whey; rennet, pepsin and chymotrypsin for milk curd coagulation; catalase, glucose oxidase and sulphydryl oxidase for milk processing are too numerous to mention. With a few minor exceptions, none have yet achieved industrial viability.

Annual amino acid production approaches half a million tonnes at a value close to US$1.25 B. About two-thirds are for human consumption, one-third for animal feeds. Japan supplies 90% of the world's amino acids. Glutamic acid, lysine, tryptophan, tyrosine, alanine and citrulline are all manufactured in

whole or part by immobilized enzymes or microorganisms. In this field, whether by continuous biological or a combination of chemical and enzymatic reactions, the Japanese are ahead of most other nations and hold manufacturing patents for all 20 commercially available amino acids.

Dominated by Japanese technology is the process whereby ribonucleic acid is hydrolized by immobilized RNAase to produce the mononucleotide flavour enhancers: inosine monophosphate (IMP) and guanosine monophosphate (GMP). For reasons undiscovered, these mononucleotides act synergistically with monosodium L-glutamate (MSG) in increasing the meaty flavour of soups, stews and sauces. The flavour enhancement of MSG is magnified 5-fold when mixed with 4% equimolar IMP/GMP. In Japan, RNA from yeast is continuously hydrolized by the RNAase of Penicillium citrinium adsorbed on a porous ceramic column. The adenosine monophosphate formed is converted by a microbial deaminase to IMP.

BREWING

Most food industries prosper by diversity: by continuously developing new products and processes for their manufacture. In contrast, the brewing industry has survived and prospered largely by improving the efficiency of production of its basic product: beer. Traditionally, beer is produced from malted cereals (mainly barley), yeast, hops and water, though only in the Federal Republic of Germany is beer brewing restricted by law to these four basic ingredients.

Mechanization of the malting process began with Galland's pneumatic malting apparatus in 1885, followed by the Saladin box with screws to turn the malt and, more recently, the Wanderhaufen moving malting couch. Though the earliest recorded experiments began in the last century, continuous fermentation in brewing has not achieved wide industrial acceptance. Only two New Zealand breweries rely significantly upon continuous fermentation.

Stewart and Russell (1985) explain the failure of continuous fermentation.

> "Essentially, batch fermentation is simple; a vessel is cleaned, sterilized and rinsed; it is filled with wort and the required quantity of yeast is inoculated. The temperature cycle can be pre-programmed and little further attention is required until it is necessary for further processing, 3 or 4 days for an ale, 7 to 10 days later for a lager. Operation by trained but not highly qualified staff is straightforward. On the other hand, continuous fermentation requires constant laboratory monitoring and complex automatic control of flow rates, temperature gradients, yeast recycle and oxygen levels. Cell morphology and fermentation gravity need regular checking. Engineering support to correct possible faults in control systems, pumps, heat exchangers and pasteurizers is required. All these must be available 24 hours a day, 7 days a week.
>
> The much more rapid flow from continuous fermentation is, in part, an illusion. It is necessary to have a reservoir of wort to feed the fermentor. Because other types of beer are likely to be produced in the same plant, a beer reservoir to accumulate the output into suitable batches for further processing is required. Although the residence time within the fermentor may be very short, this is not the economic factor that should be considered. It is the residence time in the plant that matters and this may be in excess of 24-36 hours. The use of continuous fermentation significantly reduces the flexibility of a brewery. Not all consumers drink the same beer, they drink more in summer than winter, they drink more on a hot, dry weekend than on a cold wet one. An ability to provide the required diversity of products in varying and unforeseeable amounts is a prerequisite of a successful brewing operation. Batch fermentation can meet this need for flexibility far better than a continuous process, which is best suited to the production of a high volume product at an unvarying rate."

Recently research workers at the Japanese Kirin Brewery (Onaka, et al. 1985) described how the time to brew beer of acceptable quality can be reduced from 8 days to one day. Partly fermented wort is pumped through a column reactor packed with Saccharomyces uvarum immobilized in beads of calcium alginate. By controlling the oxygen content it is claimed that undesirable diacetyl precursors can be controlled to acceptable levels. It will be interesting to see if this novel process eventually translates into a commercially viable system.

BIOTECHNOLOGY IN JAPAN

Because of the aggressive and, in some respects, unique approach the Japanese are taking in the world of biotechnology they deserve a special word. Food fermentation has been traditional in Japan for many centuries and it is probable that research on fermentation processes has been in progress for at least 100 years. Japan is the source of 21 of the 26 enzymes produced commercially and has accounted for at least 20% of all new antibiotics since 1980. Of all the new pharmaceutical products introduced each year, in the early 1960s 24% originated in the United States, 10% in Japan. By 1983, 12.5% originated in the United States, over 35% came from Japan.

The first paper on rDNA was presented in the United States in 1973; the first on a similar subject did not appear in Japan until six years later. Nevertheless, Japan's long history of traditional and industrial aerobic and anaerobic fermentations has enabled the Japanese to marshall a considerable army of experience, particularly in the design of large-scale bioreactors. These include 30-tonne capacity batch cultivation tanks and technologies based upon immobilized cells and enzymes. By applying their advanced engineering skills, combined with their highly developed sense of and experience in manipulating biological processes, the Japanese have quickly made up for lost time and are now at the world's leading edge of biotechnological development.

Japan's experience in traditional and industrial fermentations, including soya sauce, sake, and cell culture (Chlorella), extends over many centuries. Large-scale industrial fermentations and enzyme conversions started before WWII. Industrial acetone-butanol fermentations were in progress in 1940, antibiotic manufacture by 1944; glutamic acid by fermentation replaced hydrolysis of wheat gluten in the mid-1950s and the flavor enhancing nucleotides have been produced industrially since the early 1960s. From that time the range of Japanese manufactured amino acids, antibiotics and other fine chemicals has rapidly expanded.

The Japanese appear to consider biotechnology as their greatest technological hope for the future. Consequently, Japanese research and progress towards commercialization of biotechnology is accelerating over a broad range of industrial enterprises, particularly in those companies with relevant bioprocessing experience.

Unlike many other countries, the Japanese recognize what they are good at and have formulated a science policy with a clear concentration upon products derived from fermentation and related biotechnologies. Over the past 20 years, as a percentage of total R&D expenditures on pharmaceuticals throughout the world, Japan has increased its world share from 6% to 15%.

A major reason for the rapid progress made in Japan is that all government-financed research in national research laboratories and universities is directed by the Council for Science and Technology, the Chairman of which is the Prime Minister. The CST has commissioned several important studies including a basic plan for R&D in the life sciences which includes research objectives to improve the manipulation of materials carrying genetic information; and bioelectronics and biological materials as they relate to medicine, food, energy and other essential resources. In addition, the Japanese Ministry of International Trade and Industry (MITI) has established a research association for biotechnology to encourage research cooperation among 14 Japanese companies in technological development related

to the large-scale utilization of genetically manipulated plant and microbial cells. They appear as world leaders in the design and development of bio-reactors.

Japanese companies are now spending over $200 M annually on biotechnology research, about one-quarter of which is on genetically manipulated cells. The diversification of Japanese industries with experience in fermentation technologies into pharmaceuticals is worthy of special note. New or significantly expanded R&D in pharmaceuticals include chemical companies such as Hitachi and Mitsubishi; food and beverage industries including Ajinomoto, Suntory and Kirin Brewery; and textile and pulp companies such as Ashi and Toray. The cross-over integration of chemicals, food and drugs demonstrates a philosophy of growth from technological know-how rather than from a base of established markets.

The U.S. clearly regards Japan as its most formidable competitor in industrial biotechnology. Though, in absolute amounts, U.S. companies make greater investments in research and display more marketing muscle on an international commercial scale, the Japanese have gained the leading edge in industrial fermentation technologies and possess a higher proportion of trained bioengineers relative to their needs than either the U.S. or most European countries. Japanese companies place technical staff overseas as intelligence gatherers. About 20% of Mitsui's technical development staff are based in other countries.

During the 1970s, Japanese companies innovated more new drugs, mainly antibiotics, than any of their international competitors. In light of their falling profits during the past year, caused largely by increased prices and reduced government subsidies for drugs distributed in Japan, Japanese drug companies are now moving up-market to develop interferons, cardiovascular and similarly high-priced drugs.

Though they supply 85% of drugs purchased in Japan, being younger in origin, the Japanese pharmaceutical companies possess a narrower experience

and a smaller world market share than, for example, Hoffman la Roche, Merck and Glaxo. The Japanese drug companies are now moving quickly to increase and diversify their R&D expenditures; some by creating new research facilities in Japan, some by financing research in other countries. For example, Otsuka is setting up research facilities in Maryland; Ajinomoto proposes to invest US$3.8 M in cancer research at MIT. About 40 Japanese companies have established formal arrangements with bioscientific enterprises overseas in the hope of licensing new products to their larger U.S. and European partners.

Japanese, Chinese and other oriental language data bases are better designed to admit accessions from western language publications than are American and European data bases to admit entries published in oriental ideographic languages. Since, also, the Japanese make greater efforts to learn English than Anglophones make to learn Japanese, they gain better access to our publications than we to theirs. UMIST's Centre for Computational Linguistics has been awarded a major grant for the design and implementation of a prototype English-Japanese translation system. It is to be hoped it will accommodate Japanese to English translation.

Though Japanese industry invests significantly more than the government in biotechnology R&D, the government's clearly defined science and technology policy, support for universities in related research, protective licensing and import regulations all serve to stimulate Japanese industrial biotechnological development. It is estimated that the total value of industrial microbiological products made in Japan is US$50B or close to 5% of GNP, only slightly less than the total value of Japanese electronic equipment.

Japanese industries are less dependent than those in the U.S. upon venture capital. Most Japanese biotechnology companies have at least one bank as a major shareholder which provides low interest loans for R&D. The government encourages such financial institutions to establish long-term relations either by equity investment or favourable loans.

Over the past decade, in almost all industrialized countries, investment in R&D by private enterprise has outstripped that by governments. The sad exception is Britain where, since 1981, industrial support for R&D has continued to decline. A recent survey by Mori brings to light a striking

contrast between Japan and most other countries, particularly Britain, in the way private companies keep abreast of technological development. Almost one-third of Japanese companies have on their boards a scientifically competent person whose specific responsibility is technological development. In sharp contrast, company directorates which include scientists specifically responsible for advising on technology are roughly one out of every eighteen in the U.S. and one in every thirty British companies.

The Japanese intend to maintain and expand their superior cadre of scientists and technologists in the biosciences. There are close ties between Japanese industry and universities who willingly undertake applied research. Recognizing their comparative weakness in basic sciences such as molecular biology and immunology, the government and the major biotechnological companies sponsor and support overseas training for young Japanese scientists.

Though the Japanese maintain a careful cloak of secrecy over their more important industrial activities, some trends are evident. They are focussing upon protein engineering: new proteins synthesized by genetically modified cells and controlled chemical reactions. Results from crystallography, DNA hybridization and other analytical probes are fed to computers to determine amino acid configurations in existing proteins and to simulate models of protein structures with desirable functional properties. From computer models they hope to synthesize enzymes with three-dimensional structures tolerant to heat and alkalies.

Another objective is to synthesize enzymes able to biodegrade stable pesticides such as DDT. A computer determines the optimum sequence of amino acids then programs the nucleotide alignment in the DNA necessary to generate the enzyme. The ultimate goal is to introduce this rDNA into a receptive microorganism which, after multiplication would be dispersed over soils bearing heavy residues of DDT. Recognizing that lignocellulose is the most abundant and under-utilized source of biomass, they are examining microbial and enzyme conversion of cellulose and lignocellulose into edible and functionally useful carbohydrates.

Increasing investments in the life sciences include research on oncogenesis and upon phenomena related to aging, including protein metabolism, chromatine structures, cellular degeneration and abnormalities, neuro-transmitters and the hormonal control of brain and nervous systems. One of the most novel potential applications of biotechnology relates to the Japanese electronics industry. Biochips are semi-conductors consisting of specific organic molecules surrounded and stabilized by specially designed protein mono layers. Possible applications of biochip implants include the regulation of heartbeats, the control of insulin release in diabetics and the controlled functioning of artificial limbs.

The Japanese clearly intend to remain at the leading edge of biotechnological innovation and industrialization.

BIOTECHNOLOGY IN THE UNITED STATES

In the U.S., favorable tax incentives encouraged the rapid establishment and early growth of biotechnology research enterprises. The first venture capital was supplied to groups of university entrepreneurs in expectation of rapid and profitable exploitation of genetic engineering. When the early promise of rapid return was not realized, private venture capital became more difficult to attract and the biotechnology research enterprises had to seek support from industrial corporations.

Having inadequately determined the time and resources needed to realize market opportunities and failing to generate adequate cash flow, many of the new biotechnological research enterprises did not survive. The survivors are mainly those that have integrated with commercial industrial organizations. These alliances ensure a more reliable source of research capital together with intelligence from market research and feedback from the factory floor, all of which are essential if applied research is to progress to a profitable conclusion.

Many of the pioneers were overly optimistic in their expectations of when profitable products would come to the marketplace. Those that have survived may profit less from their reserch than the large multinational pharmaceutical and chemical companies with whom they have been forced to ally themselves. Between 1977 and 1983 these new bioscientific enterprises attracted more than US$350 M for research. Venture capital for scale-up and to create manufacturing and marketing facilities has been more difficult to come by and few of the original research enterprises seem likely to metamorphose into manufacturing and marketing companies in their own right.

Though the Japanese may remain up front in technological innovation, the U.S. companies will continue to dominate the marketplace. The U.S. is by far the largest consumer of pharmaceutical products and American companies dominate the U.S. market. Also, because of their large marketing forces and the high proportion (about 12%) of sales income devoted to R&D, the U.S. companies will remain sturdy defenders of their established markets.

A development which cannot be ignored is the demand and supply of scientists and engineers in the U.S. Strategic Defence Initiative (SDI), or Star Wars research in its demotic title. Defence represents 70% of total U.S. Government R&D expenditures. The comparable figure in Japan is 1.0%. Star Wars will inevitably increase defence R&D and by 1990 may absorb over 13% of all U.S. Government R&D expenditures. Equally serious is the human resource demand. By 1987, more than 18,000 scientists and engineers will be employed in SDI R&D. Recognizing the power of military influence, the excess of demand over supply may well lead to a serious brain drain from both U.S. and other nations' professional human resources.

THE ROLE OF AND RELATIONS WITH UNIVERSITIES

The patterns of biotechnology have led to new relations between university science faculties and private industry. With the possible exception of applied engineering faculties, universities have generally embraced the philosophy that "academic science must be pure and above utilitarian considerations" as a recent Canada Science Council study (1982) so stated. For the most part, universities prefer government grants, free of conditions that constrain intellectual curiosity and the freedom to publish. In recent years, in most Western nations government support of basic research in universities has steadily declined. Governments and the public alike appear less friendly to universities, the contemporary attitude being that academics should earn their keep by producing things which industry and the community can profitably use.

Much of the best expertise in molecular biology and cell biochemistry resides within academic walls. As described earlier, the promise of rich rewards has encouraged many biologists to transfer their talents from academia to commercial research enterprises. North American universities are hustling to attract profitable liaisons with the industrial sector through consulting arrangements and industrial associate programs. In return for a fixed annual fee, the companies' scientists participate in specially organized seminars, have regular contact with faculty and graduate students and are permitted first access to research results and publications.

Research contracts and research partnerships between industries and universities bear significant implications for the control of intellectual property. The research supported in universities by private industry will likely be of a more fundamental nature than the companies would carry out in their own laboratories. Since pharmaceutical companies are in business to make money and not simply to make drugs, they will expect some significant return on their investment. U.S. companies are awarding substantial contracts to universities. Washington University and Monsanto have established a five-year

renewable contract for US$23.5 M, about 30% of which will be for "fundamental research" and 70% for "special research directly applicable to human disease".

Canadian universities are formulating strategies and creating administrative units to rationalize relations and cooperative ventures with the industrial sector. Guidelines are written to ensure that industrial cooperation is consistent with established academic programs and neither compromises the universities' moral standards nor inhibits its freedom to function impartially and in the best interests of the general public.

HUMAN RESOURCES

Since most government and industrial investment in bioscientific research is devoted to the health sciences, food science and technology is at an evident disadvantage in competing for an inadequate supply of competent people. The strain is likely to be particularly severe in bioengineering. Though the proportions vary among universities, less than 10% of Canadian food science students progress beyond their first degree into post-graduate studies. A small proportion of these will likely pursue research in bioengineering. A sufficient supply of people trained in scale-up of biotechnological processes; heat and mass transfer; a comprehensive understanding of fundamental and applied biological and physical engineering principles is not apparent in Europe or North America.

LEGAL AND SAFETY REGULATIONS

This year marks the tenth anniversary of the Asilomar Conference - an historic meeting of concerned scientists, from institutions throughout the world, who gathered in 1975 to discuss the safety and advisability of continued research in the emerging field of rDNA technology.

Their primary concern was the possibility of experimental, genetically engineered organisms escaping from the laboratory to the possible danger of people and the environment. The 140 or so participants agreed by the end of the meeting that rDNA research should be continued under two kinds of voluntary safety guidelines. First, that the experiments should be conducted in containment facilities consistent with the possible hazards; second, that the experimental organisms used should be so weakened as to have little chance of surviving outside the laboratory. Magnin (IDRC 1985) poignantly describes the difficulties attendant upon scale-up of dubious organisms:

> "The safety aspects of process scale-up are especially serious when working with pathogens. Equipment on the scale needed is not designed to fit with containment hoods; the building is in effect the hood, and the production staff must work within it. Pilot plant staff are not necessarily the same people involved in the basic research. The former are usually persons more used to solving the many practical problems arising daily. Experienced persons are difficult to find and are in high demand."

The legal rights to patent products of biotechnology are somewhat obscure, particularly in the pharmaceutical field. Conventional drugs can generally be protected by patents against imitation. Many of the first generation of drugs from biotechnology are mass-produced proteins closely similar to those that occur naturally and there seems to be increasing doubt as to whether they can be exclusively owned. The large industrial giants seem indisposed to go to court over claims to exclusive rights of, for example, particular types of interferons. As The Economist (1985) pointed out:

> "The first round of (biotechnological) products are not block busters. Genetically engineered interferons have disappointed in clinical trials and caused side effects...Rather than wasting money on lawyers to try to protect patents on such products, biotechnology firms ought to think about ways of improving and cross licensing technology. The microelectronics industry did this at a similar

stage in its development and owes much of its subsequent success to its sharing, at a price, the rights to innovation and processes. It seems possible that the second and third generations of biotechnologically derived pharmaceuticals may be sufficiently novel to be as patentable as are conventional pharmaceuticals."

Government regulations that relate to health, safety and environmental protection and to the laws which govern intellectual property vary considerably among developed nations. Inconsistency among nations is particularly evident in regulations that govern the deliberate release of genetically transformed organisms into the environment.

Patent laws among countries differ on the types of biotechnological inventions that may be protected. For example, the United States permits patents for living organisms including plants and possibly animals, their products, components, methods for making or using all of them and for therapeutic and diagnostic methods. In the U.K., the FRG, France, Switzerland and Japan, patents are not permitted on plants, animals, therapeutic or diagnostic methods.

The ultimate and eventual control of the exploitation of intellectual property remains obscure. The greatest danger of a shift of genetic engineering of crop plants from the public to the private sector is that the techniques and varieties formerly embraced and retained in the public domain will become patented and proprietary. Plant varieties and the tools of genetic engineering, including genes themselves, could become protected by laws and patents. In the future, it might come about that farmers are not permitted to reproduce germplasm from their own plantations if their crop genotypes included a gene that at some stage had been patented by a multinational corporation.

Historically, genetic mutations within living organisms brought about by natural processes have evolved in a subtle and relatively slow manner.

Consequently, not until the advent of food irradiation were regulatory authorities required to give serious thought to genetic mutation and the potential hazards of the novel and often unpredictable products of free radical reactions.

The potential impact of induced alterations in DNA nucleotide sequences and gene cloning seriously upsets the regulatory agencies' gradual and methodical adjustment to evolutionary change. In the US FDA category of food ingredients "generally recognized as safe by experts qualified by training and experience to judge their safety" (the GRAS category) "safe" is defined as exhibiting "reasonable certainty of no harm". The new techniques of genetic manipulation are proceeding at a rate that precludes parliaments and regulatory agencies from following their normal leisurely approach to the attendant issues of comparative safety.

Late in 1984 the Office of Science and Technology Policy (OSTP) published the U.S. Government's policies towards biotechnology. The document, which is 51 pages long, describes as its purpose: "to provide a concise index of U.S. laws related to biotechnology; to clarify the policies of the major regulatory agencies that will be involved in reviewing research and products of biotechnology; to describe a scientific advisory mechanism for assessment of biotechnology issues; to explain how the activities of the federal agencies in biotechnology will be coordinated". It goes on to state that biotechnology will be regulated in a manner that will not "stifle innovation and impair the competitiveness of U.S. industry".

Many concerns about safety have been raised, including the possible effect of genetic manipulations on the potential virulence of altered microorganisms and the ability of new and potentially harmful organisms to obtain selective advantages. It has been noted that the molecular structure of some biotechnologically derived drug products are different from those of the naturally occurring active molecules. To determine to what degree these differences in chemical composition will affect biological activity or

immunogenicity calls for extensive chemical and biological testing prior to licensing. When a genetically modified microorganism is used to produce a traditional and familiar end product more efficiently it will be necessary to ensure that it does not simultaneously produce unfamiliar and unusual by-products.

Following publication of the OSTP's policies on biotechnology, Congressman John Dingell stated that he intends to preside over a thorough review of the adequacy of all the laws applicable to biotechnology; and how they will be interpreted and applied in the implementation of biotechnology programs. Cell fusion, embryo transplants and elaborate gene transfers may eventually give rise to intergeneric plant hybrids and animal chimeras widely different from plants and animals currently inspected under established food and drug regulations. Decisions will have to be made as to what extent such wide intergeneric hybrids must be regarded as novel foods requiring new regulatory protocols.

NOVEL FOODS

The safety of novel foods is being addressed by specialist committees in the United States, the United Kingdom and several other countries. Particular attention must surely be given to novel foods derived from fermentation of unusual raw materials, such as lignocellulose degraded by lignocellulytic funghi and other microorganisms quite unfamiliar to human diets. Any suggestion that novel fermentation products should supplement the diets of poor people in developing countries, debasing them to the status of experimental guinea pigs for the rest of mankind, is surely unworthy of responsible consideration.

RESPONSIBLE MANAGEMENT

On the last occasion I was privileged to speak to the North of England Branch of the IFST, I expressed concern with contemporary trends in ownership and management of food corporations (Hulse, 1984). Antipathy towards research and technological development is evident among accountants whose vision reaches only to the bottom line of the latest financial statement: those who regard research as an expense, not as an investment. Particularly worrisome are the financial holding corporations which acquire assortments of technologically unrelated companies and manage them as they would a stock portfolio. The strength of Japanese industry lies in its commitment to research and its disposition to promote scientists and technologists to senior management positions.

The traditional fermentation industries: baking, brewing and dairying, were created by craftsmen with an intimate understanding of their trade. With pragmatic cognizance of their constraints they were better able to assess their opportunities than were accountants and corporate lawyers.

It was Montesquieu who wrote: "Success depends upon knowing how long it takes to succeed." The short history of the new biotechnologies makes it exceedingly difficult to give reliable forecasts of technological fulfillment. Such forecasts are beyond the ken of corporate accountants and lawyers. Sadly, the vision of many research scientists does not extend far beyond the laboratory door. The future of the food, pharmaceutical and related biotechnological industries requires a new breed of management: people who can conceive and integrate the total complement of resources needed to successfully develop, manufacture, and safely and economically distribute the products of biological innovation. To provide this essential new class of scientific managers presents a unique, and one would hope, stimulating challenge to all universities.

Thoreau wrote: "He is not a true man of science who does not bring human sympathy to his studies." The Book of Proverbs counsels that "without vision the people will perish".

Guided by a new and carefully cultivated group of men and women who combine scientific management with a vision refined by human sympathy, the emerging biotechnologies may benefit mankind immeasurably. But in incompetent or irresponsible hands the outcome will be at best disappointing; at worst disastrous.

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