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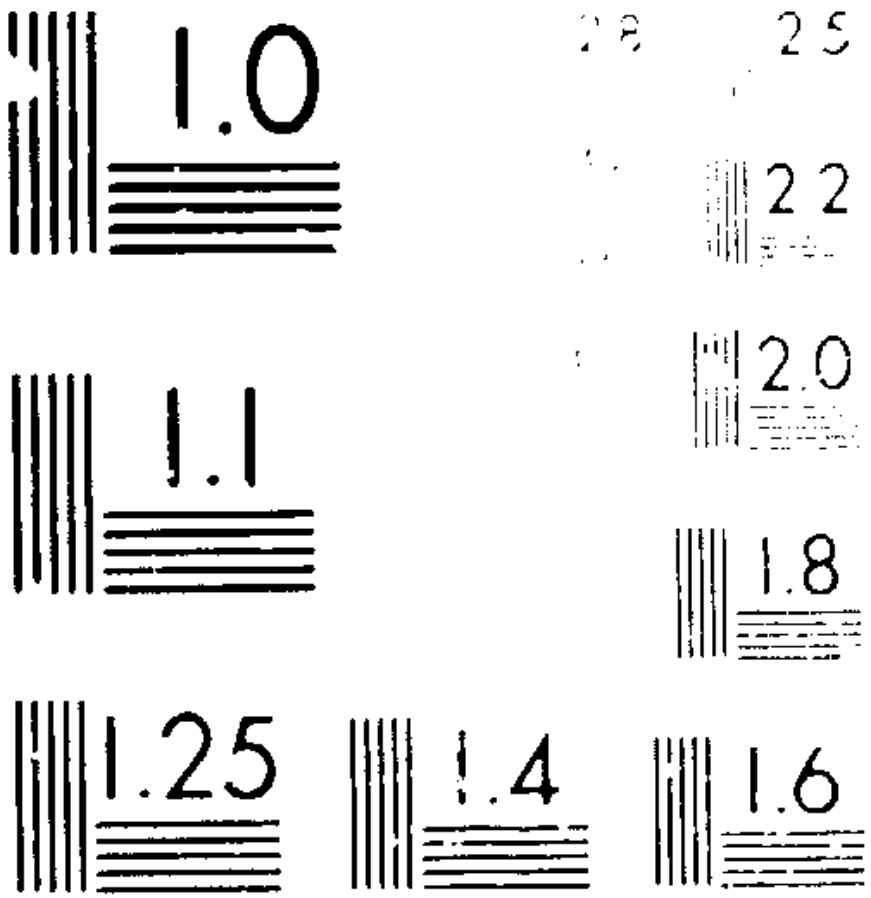
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Distr.
LIMITED

UNIDC/IS.269
21 December 1981

ENGLISH

UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

THE IMPACT OF GENETIC ENGINEERING ON INDUSTRY*

prepared by

UNIDO Technology Programme

* Based on "Impacts of applied genetics: micro-organisms, plants and animals", Office of Technology Assessment, United States Congress, Washington, D.C., United States of America (OTA-HR-132, April 1981).

V.81-31636

Abbreviations

AA	amino acids
EOR	enhanced oil recovery
FDA	Food and Drug Administration (United States)
ICI	Imperial Chemical Industries
NIH	National Institutes of Health (United States)
ppm	parts per million
R+D	research and development
rDNA	recombinant deoxyribonucleic acid
SCP	single-cell protein

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PREFACE

UNIDO's programme of technological advances aims at sensitizing developing countries to the potentials and limitations of emerging technological advances and strengthening their capabilities to make use of such advances, whenever appropriate. The programme includes activities in the field of genetic engineering and biotechnology. A meeting of eminent experts in this field was held at Vienna from 4 to 6 February 1981 and, following one of the meeting's recommendations, a group of experts prepared a report on the establishment of an International Centre for Genetic Engineering and Biotechnology. Future activities envisage inter alia national-level workshops on the potentialities of genetic engineering and biotechnology for industrial development for industrialists, scientists and policy-makers of developing countries.

In order to provide developing countries with information on ongoing assessments of genetic engineering and its impact on industry, the secretariat of UNIDO considered it useful to prepare a paper based on "Impacts of applied genetics: micro-organisms, plants and animals" (April 1981) prepared by the Office of Technology Assessment, United States Congress, United States of America, but covering industrial sectors only.

The paper has been prepared by the UNIDO secretariat for the purpose stated earlier and does not constitute an official paper of the Office of Technology Assessment.

INTRODUCTION

In recent years, biotechnology in general, and genetic engineering in particular, have shown that they could contribute to filling some of the most fundamental needs of humankind.

Biotechnology is the industrial process which utilizes living organisms or their components. Genetic engineering concerns the directed manipulation of the genetic material itself. This process, which involves recombinant DNA (rDNA) and the chemical synthesis of genes, could increase the size of the gene pool for any one organism, thus making available genetic traits from diverse populations. Genetic engineering can help improve the speed, efficiency and productivity of biological systems. It uses a technique, at the laboratory level, which allows modification of the hereditary functions of the cell. The population of the altered identical cell that grows from the first unchanged micro-organism is, in turn, used for various industrial processes. It is within this framework that the impacts of applied genetics in the various industries is examined.

Regardless of the industry, the same three preconditions must be met before genetic technologies can become commercially feasible. They are:-

(a) a useful biological product;
(b) a useful biological fermentation approach to commercial production;
(c) a useful genetic approach to increase the efficiency of production.

All three conditions are interrelated and can be met in any order. The demonstration of usefulness, however, can begin with any of the three. Thus, the commercial potential varies with each product. In some cases, the usefulness is already shown and the usefulness of genetic engineering must be proved. In others, genetic engineering makes production at the industrial level possible, but the market is not established, and in others, feasibility is the major problem.

The time horizons (5, 10, 15, 20 years) for the commercialization of various products using genetically engineered micro-organisms are presented in an annex. The estimated value of these products is $24 billion.

I. FERMENTATION TECHNOLOGIES

A. General View

The oldest user of biotechnology is the food industry where micro-organisms are used to ferment food and beverages. It is estimated that approximately 700 companies throughout the world use fermentation technologies to produce a variety of products. Originally, fermentation technology involved the use of bacteria to make yoghurt or of yeast to ferment wine. Recently, however, fermentation technology utilizes cells from higher plants and animals under growth conditions known as cell or tissue culture. In all cases, large quantities of cells with uniform characteristics are grown under defined controlled conditions.

In its simplest form, fermentation consists of mixing micro-organisms with a solution and allowing the components to react. The more sophisticated large-scale process requires control of all the variables so that fermentation proceeds smoothly and the process can be reproduced with the identical quantities of starting material.

Generally, products obtained from fermentation can also be produced chemically and less often, could be isolated by extraction from whole organs or organisms. A fermentation process is attractive when the analogous chemical process requires more steps to complete the conversion. Furthermore, a chemical process would invariably proceed via a series of intermediates which have to be extracted and purified in turn before they are used in the next step. whereas during fermentation, all steps take place within the micro-organisms.

3. Enzyme Technologies

Fermentation by live cells has provided the basis for designing fermentation processes based on isolated enzymes. A single enzyme situated within a living cell is needed to convert a raw material into a product. Now if the enzyme responsible for the conversion is identified, it can be extracted from the cell and used in place of a living cell. The purified enzyme functions exactly as the cell, breaking down the raw material in the absence of a micro-organism . An enzyme which can convert a raw material to a product inside the cell could also do this outside the cell.

Although more than 2,000 enzymes have been discovered, less than 50 are of industrial importance. However, two major features

make them attractive; their specificity and their ability to function under relatively mild temperature and pressure conditions.

At the moment, both whole cells and isolated enzymes are being used and it is difficult to predict which will be more prominent in the future. Although both have their advantages and disadvantages, the role of genetic engineering in the future of the industry will be partly determined by which is chosen. With isolated enzymes, genetic manipulation can increase the supply of enzymes whereas with whole organisms a variety of manipulations is possible in constructing more productive strains.

C. The Relationship of Genetics to Fermentation

Applied genetics and fermentation technology are closely linked because isolating a suitable species of micro-organism is the first step in developing a fermentation technique. Until recently, geneticists had to search for an organism that already produced the desired product. However, through genetic engineering micro-organisms can be made to produce substances beyond their "natural" capabilities. The most striking advances have appeared in the pharmaceutical industry where human genes have been transferred to bacteria to produce insulin, interferon, growth hormone, etc.

The current industrial approach to fermentation technologies addresses two problems. Initially, whether a biological process can produce a particular product and, secondly, what micro-organism has the greatest potential and how the desired characteristics can be engineered for it. Finding the desired micro-organism and improving its capability has now become a fundamental and important aspect of the fermentation industry.

II. The PHARMACEUTICAL INDUSTRY

A. General View

The pharmaceutical industry, which was the last to adopt traditional fermentation techniques, has been the first industry to extensively use rDNA and cell fusion techniques. Genetic engineering for the production of pharmaceuticals has two goals:

(a) to increase the level or efficiency of the production of pharmaceuticals of proven or potential value;

(b) to produce totally new pharmaceuticals and compounds not found in nature.

The first goal has had the strongest influence on the industry. It has been almost axiomatic that if a naturally occurring organism can produce a pharmacologically valuable substance, genetic manipulation can increase the output.

B. Potential Uses of Molecular Genetic Technologies

Polypeptides (proteins), which are the end-products of genes, include peptide hormones, enzymes, antibodies and certain vaccines. Producing them has been the goal of most recent work in genetic engineering. However, it is merely a matter of time before complex non proteins like antibiotics can be made through rDNA techniques.

1. Hormones

Hormones are the messenger molecules that help the body co-ordinate the actions of various tissues. The most advanced application of genetics today is in the field of hormones. Attempts at synthesizing human peptide hormones (e.g. insulin and growth hormone) gave genetic engineering the necessary impetus in that field.

There are four technologies for producing polypeptide hormones:

(a) extraction from human or animal organs, serum or urine; chemical synthesis;

(b) production by cells in tissue culture;

(c) production by microbial fermentation after genetic engineering.

One major factor in deciding which technology is best for which hormone is the length of the hormones amino acid chains. The low molecular weight peptides can be chemically synthesized relatively easily. Thus, the chemical synthesis of hormones up to 32 amino acids (AA) in length can be competitive with those derived from biological sources. Since polypeptide hormones can also be synthesized genetically, the practicality of doing so must be assessed on a case-by-case basis. The main criteria necessary for assessing the practicality of one method vis-à-vis the others are:-

(a) cost of raw materials;

(b) the cost of separation, purification and removal of contaminants;

(c) labour and equipment costs;

(d) costs and suitability of comparable materials gathered from organs or fluids obtained from animals or people.

(a) Insulin

Insulin is composed of two chains (A and B) of amino acids. Work on the genetic engineering of insulin has proceeded quickly and both chains of human insulin have been synthesized. It is worth noting that while 2,000 l of fermentation brew would yield 1 g. of purified insulin, 16 g. of animal pancreas would be required to produce the same amount. Current research is under way to increase the yield (the average diabetic requires 2 mg of animal insulin per day).

Genetically synthesized insulin, however, is not yet ready for commercial use. The drug has to be approved by the United States Food and Drug Administration (FDA) and marketed as a product as least as good as the insulin product produced conventionally. The clinical rationale behind using a human insulin is due to the differences in structure among insulins produced by different species. It remains to be seen how many patients will be better off with human insulin and whether the side-effects of diabetes, retinopathy and nephropathy will be minimized.

(b) Growth Hormone

Growth hormone is another polypeptide hormone awaiting approval by the FDA. It is a single chain polypeptide, 191 to 198 AA in length and is essential for postnatal human growth. The secretion of insulin is stimulated by growth hormone and the action of growth hormone in the body depends on the presence of insulin. Human growth hormone, apart from correcting dwarfism, is also found to be of therapeutic value in other areas, namely:-

(i) senile osteoporosis (bone decalcification);

(ii) other nonpituitary growth deficiencies such as Turner's syndrome;

(iii) intrauterine growth retardation;

(iv) bleeding ulcers that cannot be controlled by other means;

(v) burn, wound and bone-fracture healing.

The preparation of micro-organisms with the capacity for synthesizing growth hormones has been achieved.

(c) Other Hormones

Other polypeptide hormones where rDNA synthesis is being attempted include:-

(i) Parathyroid hormone (84AA) - may be useful for bone disorders, e.g. osteoporosis;

(ii) Nerve growth factor (118 AA) - influences development, maintenance and repair of nerve cells and thus would be significant for nerve restoration in surgery;

(iii) Erythropoietin - glycopeptide mainly responsible for blood cell development, may be useful for haemorrhages, burns, anaemia and other haemotologic conditions.

2. Immunoproteins

Immunoproteins are the class of proteins which are part of the immune system, e.g. antigens, interferons, cytokines and antibodies. Since polypeptides are so relevant to immunology, developments in genetic engineering will affect the entire field. Hence, genetic engineering is expected to play a major role in controlling immunological functions, particularly as it is the only known method of synthesizing many of the agents that comprise immunopharmacology.

(a) Antigens (Vaccines)

Genetic engineering could produce harmless vaccines to fight infectious diseases and scientists expect this areas to benefit greatly from genetic engineering.

Immunity from live vaccines is greater than that from non-living antigens. This is thought to be because a living micro-organism can create more antigen over a longer period of time, i.e. provide a continuous "booster shot" effect. Thus, genetically engineered antigens are expected to provide a stronger and more sustained effect than the conventional vaccines. Additionally, the conventional vaccines, consisting of killed micro-organisms, produce a certain amount of side-effects.

Other vaccines which are expected to be produced via genetic engineering are those to combat influenza, polio, diphtheria, hepatitis and foot-and-mouth disease.

Genetic engineering could lead to other uses of antigens as well: vaccines against parasites(e.g. hookworm, or malaria), immunization regarding cancer treatment and counteracting abnormal antibodies against healthy tissues (e.g. multiple sclerosis).

(b) Interferons

Interferon is a protein which is produced by a variety of cells when infected with a virus. It inhibits viral reproduction and induces resistance in host cells. Additionally, interferon has been found to have at least 15 other biochemical effects partly involving other elements of the immune system.

Initial studies have shown interferon to be promising in the treatment of viral diseases, e.g. rabies, hepatitis, shingles and various herpes infections. Currently, several production methods are being investigated, namely extraction from white blood cells, tissue culture production and rDNA. rDNA is thought to be the key to mass production.

Since recent studies have shown interferon to be promising in cancer treatment, interferon production has received tremendous attention.

(c) Lymphokines and Cytokines

Lymphokines and cytokines are regulatory molecules studied in immunology (interferon is often considered to be a lymphokine that has been sufficiently characterised to be considered independent). Lymphokines, which are biologically active soluble factors produced by white blood cells, are throught to be directly involved in the immune response system. Cytokines, which have similar effects to lymphokines, include several compounds associated with the thymus gland.

Both lymphokines and cytokines are believed to be effective in treating cancer and genetic engineering is a useful tool for synthesizing them.

(d) Antibodies

Antibodies are proteins found mainly in the blood system. They are produced normally or in response to an antigen and characterised by a specific reactivity with its complementary antigen. Previously, all antibodies were produced from human or animal blood cells. However, now they can be produced using rDNA. This new high level of purity, not previously possible, produces antibodies which are more specific, and thus more effective. The application of antibodies in medicine includes diagnostic testing, improving acceptance of organs after transplants, and fighting certain types of cancer.

(e) Enzymes and Other Proteins

(i) Enzymes

Enzymes, the biochemical catalysts, play a small role in therapeutic medicine. Biologically, they are considered to be potent, versatile and diverse. Conventional methods of obtaining enzymes are either via extraction from human blood, urine, or organs, or production by micro-organisms. rDNA offers an efficient and more economic method of synthesising enzymes.

The main use of enzymes in medicine is to treat haemophilia. The most common agents are Factor VIII and Factor IX both of which are derived from human blood plasma. However, the risk of hepatitis associated with human plasma-derived products is very high. Thus, the need for high quality pure enzymes which could be derived from rDNA is strong.

Another enzyme, urokinase used for removing blood clots (which could lead to strokes, myocardial infarctions, etc.) is currently produced either from urine or tissue culture. Here too, rDNA could provide a more economical method of producing the enzyme.

(ii) Other Proteins

The structural proteins such as the collagens (the most abundant protein in the body), elastins, keratins, albumins, globulins and many others could be produced through genetic engineering.

However, their widespread use in medicines has to be established before warranting rDNA synthesis on an industrial scale. One notable exception, however, could be serum albumin which is a protein in blood plasma. Its main therapeutic use is to reverse the effect of shock. It is envisaged that the United States Department of Defence, for example, may find it valuable to have a ready source of human serum albumin rather than having to depend on blood donors.

(iii) Antibiotics

Antimicrobial agents for the treatment of infectious diseases have been the largest selling prescription pharmaceuticals in the world for the past three decades. Most of these agents are antibiotics - antimicrobials naturally produced by micro-organisms rather than by chemical synthesis or by isolation from higher organisms. However, one major antibiotic, chloramphenicol - originally produced by a micro-organism, is now synthesized by chemical methods. The field of antibiotics, in fact, provides most of the precedent for employing microbial fermentation to produce useful medical substances.

Antibiotics are complex, usually non-protein substances, which are generally the end-products of a series of biological steps. Not a single antibiotic has had its complete biosynthetic pathway elucidated. This is partly because there is no single gene that can be isolated to produce an antibiotic. However, mutations can be induced within the original micro-organism so that the level of production can be increased.

Other methods can also increase production and possibly create new antibiotics, for example, microbial mating. The technique of protoplast or cell fusion provides a convenient method for establishing a recombinant system in strains, species, and genera that lack an efficient natural means for mating. For example, as many as four strains of the antibiotic-producing bacterium Streptomyces have been fused together in a single step to yield recombinants that inherit genes from four parents. The technique is applicable to nearly all antibiotic producers. It will help combine the benefits developed in divergent lines by mutation and selection. The value of protoplast fusion, therefore, lies in potentially broadening the gene pool.

Recombinant DNA techniques are also being examined for their ability to improve strains. Many potentially useful antibiotics do not reach their commercial potential because the micro-organisms cannot be induced to produce sufficient quantities by traditional methods. The synthesis of certain antibiotics is controlled by plasmids, and it is believed that some plasmids may non-specifically enhance antibiotic production and excretion.

(iv) Non-protein pharmaceuticals

In both sales and quantity, over 80 per cent of the pharmaceuticals produced today are not made of protein. Instead, they consist of a variety of organic chemical entities. These drugs, except for antibiotics, are either extracted from some natural plant or animal source or are synthesized chemically.

Developments based on genetic techniques to increase the production and secretion of key enzymes could substantially improve the economics of some presently inefficient processes. Currently, assessments are being carried out by various companies to determine which of the many non-protein pharmaceuticals can be manufactured more readily or more economically by biological means.

(v) Impacts

It is worth emphasizing at this point that although genetic engineering provides an efficient and economic method for synthesis of pharmaceuticals, both the United States National Institutes of Health (NIH) and the FDA have to assess and approve each drug before it can be made commercially available.

By making a pharmaceutical available, genetic engineering can have two types of impact. Firstly, pharmaceuticals which already have medical promise will be available for testing (e.g. interferon). Secondly, other pharmacologically active substances which have no known use will be easily available for researchers to investigate their potential.

The ability of the new technology to increase and improve vaccine production through rDNA is indeed a boon to the people of the developing countries. Antibody-based diagnostic tests, developed through rDNA may include early warning signs for cancer.

Whether new pharmaceuticals are produced or new production methods for existing pharmaceuticals devised, future sources for the drugs may change. Currently, the sources are diverse plants, animal organs, tissue culture, cells and a range of raw materials, but with genetic engineering, the choice is narrower.

Given the above assumption, the immediate direct economic impact of using genetic engineering in the industry can be estimated in billions of dollars. While the indirect impact (sales for suppliers, savings due to decreased sick days, etc.) is estimated to be several times that value.

III. THE CHEMICAL INDUSTRY

A. General View

The organic chemicals initially used by humans to make useful materials, (e.g. cotton, linen, silk, leather, dyes, etc.) were all obtained from animals and plants and thus were renewable sources. At the beginning of the twentieth century petroleum, which was relatively cheap, began to be widely used as a raw material. However, due to the rising cost and rapidly decreasing sources of petroleum, the chemical industry is looking for alternatives. Most industrial analysts, therefore, expect a shift back to the natural renewable resources referred to as biomass. Genetic engineering will probably play an important role in enhancing the possibilities by allowing biomass and carbohydrates to be converted into chemicals. Biology is thus expected to have a dual function of providing both the raw materials and a production process for the chemical industry.

The chemical industry is one of the largest and most important in the world today. The main raw materials are petroleum, coal, minerals (phosphate, carbonate) and air (oxygen, nitrogen). About two thirds of the industry is devoted to inorganic chemicals (lime, salt, ammonia, chlorine, hydrogen chloride, carbon dioxide) while the remaining one third, which is the focal point for biotechnology produces organic chemicals (plastics, synthetic fibres, synthetic rubber, organic solvents).

A few industrial production processes utilise fermentation, e.g. the production of citric and lactic acids and various amino acids. Citric acid, which is one of the major industrial acidulants, is commercially produced by the mould Aspergillus niger. Lactic acid production is based on the bacterium species Lactobacillus. Most, if not all, of the amino acids have been the target for microbial production. The two important ones in the chemical industry produced by fermentation are glutamic acid (as a base for monosodium glutamate - a flavour enhancer) and lysine and L-lysine (as animal feed additives).

B. New Process Introduction

The introduction of biotechnology and genetic engineering to the chemical industry ought to be regarded not as the creation of a new industry but as the revival of an old one. The main advantages are envisaged as the use of renewable resources, less extreme conditions, use of single-step production processes and a reduction in pollution (e.g. a micro-organism could be constructed to directly convert cellulose in wood into ethanol).

1. Renewable Sources

During photosynthesis, plants convert carbon dioxide into carbohydrates. Part of the carbohydrates are, in turn, converted into the plant's energy requirements, while the rest are accumulated as starch, cellulose, lignins and other materials collectively termed as biomass. Now genetic engineering has the potential to alter the chemical industry's dependence from petroleum-based raw materials to biomass. However, since the cost of carbohydrates and other biological materials is also increasing the industry may be cautious at this stage

2. Physically Milder Conditions

Chemical reactions can be accelerated by increasing the temperatures and pressure or using a suitable catalyst. On the industrial scale, however, a catalyst, in addition to high temperatures and pressures, is necessary to produce most organic compounds. Enzymes can accelerate reactions without extreme [illegible] conditions. Such reactions occur in dilute aqueous solution [illegible] pH, ambient temperatures and atmospheric pressure.

3. One Step Production Method

The chemical synthesis of compounds, invariably a multi-step process, involves isolation and purification of each intermediate before it can be used. Furthermore, the chemicals used and the by-products of the reaction are often toxic and require special disposal. In biological systems, the conversion is a single step process (although several steps could occur within the micro-organism) minus the unnecessary labour of purification.

4. Reduced Pollution

Chemical reactions, both catalytic and non-catalytic, are not ordinarily limited to making the end-product exclusively. The formation of side-products and/or by-products and the incomplete conversion of starting material are common phenomena. When side-products and by-products are of no value or when unconverted raw materials cannot be economically recycled, waste disposal and pollution problems arise. A genetically engineered organism, however, can be product specific. Additionally, biological processes in general simplify product recovery. Furthermore, waste products, if created by biologically-based chemical processes, tend to be biodegradable as well as useful sources of nutrition.

The United States Environmental Protection Agency (EPA) estimates that chemical and allied industries, in the United States Government and industry together, will spend about $26 billion during the decade 1977-1986 to control air and water pollution. It has been speculated that if just five per cent of the industries used genetic engineering, the monetary saving on pollution could be $100 million per annum.

C. Industrial Chemicals That May Be Produced by Biological Technologies

1. Overview

Two questions are important when assessing the feasibility or desirability of producing various chemicals biologically. They are:

(a) which compounds can be produced biologically (even theoretically)?

(b) which compounds may be primarily dependent on genetic technology, given the costs and availability of raw materials?

Virtually all organic compounds can be produced biologically. Three variables affect the answer to the second question: the availability of an organism for the conversion, the cost of the raw material and the cost of the production process.

The constraints vary from compound to compound. However, although the role of genetics must be on a product-by-product basis,

a few generalizations can be made. Overall, genetic engineering will have an impact on three processes:

(a) Aerobic fermentation - which produces enzymes, vitamins, pesticides, amino acids, nucleic acids and other speciality chemicals - is well established and should be allowed to grow. Production of both complex biochemicals (antibodies, growth factors and enzymes) and less complicated molecules (amino acids and nucleotides) is expected to increase;

(b) Anaerobic fermentation - which produces organic acids, methane and solvents - is an industrially expanding area. The main constraint on the production of other organic acids and solvents is a cheaper method to convert cellulose into fermentable sugars;

(c) Chemical modification of both aerobic and anaerobic fermentation products has promise. Biological technologies which operate at atmospheric pressure and ambient temperatures can replace the harsher physical conditions of the chemical technologies. This has already been attempted for ethylene glycol production which is awaiting patent approval.

2. Fertilizers, Polymers and Pesticides

(a) Fertilizers

The industrial production of nitrogenous fertilizers requires large amounts of gaseous ammonia (which in turn is made from petroleum by-products) and extremely high temperatures and pressures. The enzymatic conversion of atmospheric nitrogen to ammonia, nitrogen fixation, occurs in bacteria associated with the roots of leguminous plants. Apart from the enzyme's sensitivity to oxygen and the lack of understanding about its mechanism, the microbial production of ammonia is not yet considered economically viable. However, the genes for nitrogen fixation have been transferred into yeast thus opening up the possibility that agriculturally useful nitrogen can be made by fermentation.

(b) Polymers

A large part of the chemical industry is involved in polymer production which is based on petroleum and its by-products. Since polymers are built from monomers, which are chemically simple and available in relatively high yield from petroleum, their microbial production in the near future is not expected. However, the essential impact of biotechnology on polymer production is expected to be considerable. Most of the important constituents of cells are polymers (proteins, polysaccharides, polynucleotides, etc.). Since cells normally assemble polymers with high specificity, the ideal industrial process would have to imitate the biological process in every possible respect. A micro-organism would have to convert a raw material into a monomer, followed by polymerisation and then finally to form the end-product. A more likely application would be the development of new monomers for specialized applications. Since polymer chemistry is concerned with studying how their properties can be modified, it is conceivable that biotechnology could enable the modification of both function and form.

(c) Pesticides

The largest market in pesticides involves the chemical and microbial control of insects. Although microbial insecticides have been around for years, they comprise about five per cent of the market. However, recent successes in developing viruses and bacteria which produce disease in insects, and the negative publicity given to chemical insecticides, have encouraged the use of microbial insecticides.

Of the 15,000 known species of insects, only 200 are sufficiently harmful to warrant control or destruction. Fortunately, most of them are sensitive to certain micro-organisms which, if they are not toxic to humans, non-target animals and plants, could be commercially utilized as insecticides. Approximately 100 known species of bacteria are pathogenic to insects. But only three (Bacillus popilliae, Bacillus thuringiensis, and Bacillus moritai) have been developed into commercial insecticides.

Genetic engineering should make it possible to construct more potent bacterial insecticides by increasing the dosage of the genes that code for the synthesis of the toxins involved. It may also be possible to produce mixtures of genes capable of directing the synthesis of various toxins.

D. Constraints on Biological Production Techniques

The main obstructions to using biological production technology are associated with biomass; these include:

(a) competition with food needs for starch and sugar;

(b) cyclic availability;

(c) bio-degrability and associated storage problems;

(d) high moisture content for cellulosics and high collection and storage costs;

(e) mechanical processing for cellulosics;

(f) the heterogeneous native of cellulosics (mixtures of cellulose, hemicellulose and lignin);

(g) the need for disposal of the nonfermentable portions of the biomass.

For food-related biomass sources (sugar, corn, sorghum) there are few, if any, technological barriers for conversion to fermentable sugars.

However, if the fermentation of sugars is to be as profitable as their incorporation into food, subsidies will be required. For biomass sources (agricultural and municipal wastes, wood) technological barriers exist in collection, storage, pretreatment, fermentation and waste disposal. Furthermore, biomass has to be transformed into sugars by either chemical or enzymatic processes before fermentation can begin.

A second major problem is concerned with the purification stage. Most fermentation products are in dilute solutions and concentration is energy-intensive.

Although developments in genetics show tremendous promise for creating more versatile micro-organisms, they do not by themselves produce cheaper fuels or plastics. However, genetic engineering is expected to reduce the production costs in many steps.

E. Impacts

1. Overview

Cost of raw materials may become cheaper than the petroleum now used (especially if cellulose conversion technologies can be developed). The source of raw materials would be broader, especially since several types of biomass could be interchanged when necessary. Raw materials like organic wastes, could be processed both to produce products and reduce pollution. But, the impact on total imported petroleum will be low.

Impacts on the process include relatively cheaper production costs for selected compounds. Additionally, milder physical conditions can be used suggesting the process might be safer. Although chemical pollution may be lower alternate methods of disposal or new ones must be found for the micro-organism now used.

Impacts on products include both cheaper existing chemicals as well as completely new products. Furthermore, new uses for enzymes may expand and drive this sector of the industry.

2. Impacts on other Industries

Although genetic engineering will and can develop new techniques for synthesising many substances, the direct displacement of any present industry appears to be doubtful. Genetic engineering should be considered as another industrial tool. It is misleading to refer to "genetic

engineering companies" as a new industry; the companies arose mainly to convert micro-organisms with little commercial use into micro-organisms with commercial potential.

Since genetic engineering is a relatively small-scale laboratory operation, genetic engineering companies will continue to offer services to companies where such expertise is lacking. Additionally, suppliers of genetic raw materials may decide to expand into the production of genetically engineered organisms. Finally, companies are beginning to examine their by-products or waste products as possible sources of conversion into useful products.

3. The Social Impacts of Local Industrial Activity

Despite the extensive media coverage of rDNA and associated genetic engineering research, there is little, if any, evidence that people who live near such companies are concerned about possible hazards. Companies, so far, have adhered to the NIH Guidelines.

4. Impacts on Manpower

Two types of impacts on workers can be expected:

(a) The creation of jobs that replace those held by others (e.g. a worker in chemical production may be replaced by one producing the same product biologically);

(b) Creation of new jobs.

Workers in three categories would be affected:

(a) Those involved in the fermentation production phase of the industry;

(b) Those involved in the R+D phase of the industry, particularly professionals;

(c) Those in support industries.

The number of workers involved in the production phase of biotechnology represents the major impact of genetic engineering. Estimates of the number of totally new jobs that would be created are speculative.

IV. THE FOOD PROCESSING INDUSTRY

A. General View

Genetics can be used in the food processing industry in two ways. Primarily to design micro-organisms that transform inedible biomass into food for human consumption or animal feed. Secondly to design organisms that aid in food processing, either by acting directly on the food itself or by providing materials that can be added to food.

Traditionally, micro-organisms were used to stabilize, flavour and modify properties of food. Recently, efforts were made to control microbial spoilage and to ensure that foods were free from micro-organisms that may be hazardous to public health. These are the two major ways in which microbiology has been useful.

B. Single-Cell Protein (SCP)

1. Introduction

Interest in augmenting the world's supply of protein has focused attention on microbial sources of protein as food for both animals and humans. Bacteria and/or yeast have been grown in large quantities to supply SCP for consumption. The protein can either be consumed directly as part of the cell or be processed into fibres. The idea of using SCP as animal feed or human food is not new; yeast has been used as food protein since 1900. Recently, however, there has been a sudden increase in research on SCP and in the construction of large-scale plants for its production, especially yeast production. Soyabean, too, is another quick source of protein and soyabean products are rapidly increasing in popularity. While significant research is directed at the genetic improvement of soyabeans, genetic techniques are also being investigated to increase the production of SCP. Thus, ironically, the same tool (genetic engineering) encourages competition between the two.

2. Genetic Engineering and SCP Production

Many substances are being considered as raw materials for conversion to SCP.

(a) Petroleum-based hydrocarbons - until recently the n-alkanes (petroleum by-products) were suitable raw materials for SCP production. At British Petroleum, mutants of micro-organisms with an increased protein content

have been isolated. Mutants also have been found with other increased nutritive values, e.g. vitamin contents.

(b) Methane or methanol - relatively few genetic studies have been directed at investigating the genetic control of the microbial use of methane or methanol. However, Imperial Chemical Industries (ICI) has altered the genetic make-up of the bacterium so that the organisms can grow more readily on methanol. The increase in growth provides an increase in protein and has made production less expensive.

(c) Carbohydrates - many carbohydrate substrates have been investigated. Forests are the most abundant carbohydrate source (as cellulose). But the cellulose must be transformed by chemical or enzymatic pretreatment into glucose (the carbohydrate) before it can be used by micro-organisms. Many of the SCP processes that use cellulose employ organisms that produce the enzyme cellulase, and this degrades cellulose to glucose.

Recently, there have been some significant studies on the production of cellulose by micro-organisms. Some studies have also been done on creating fungal mutants that produce excess amounts of cellulose.

3. Commercial Production

It is estimated that 2 million tons of SCP are produced annually in the world. Most of this comes from cane and beet molasses, and about 500,000 tons from hydrolised wood wastes, corn trash and paper mill wastes.

It is possible to design integrated systems to couple food production (or other "product" production) with SCP production from wastes. For example, the waste sawdust from the timber industry could be a source of cellulose for micro-organism. The successful genetic engineering by ICI of a micro-organism to increase the usefulness of one raw material (methanol) is the beginning of similar attempts for other raw materials.

While SCP can be obtained from a wide variety of micro-organisms and raw materials - the nutritional value and safety of each micro-organism vary widely. So do the costs of competing protein sources in regional markets. Thus it is not possible to accurately predict the extent to which SCP will displace traditional protein products. Displacements will continue to occur on a case-by-case basis.

C. Genetics in Brewing, Baking and Winemaking

The micro-organism of the greatest significance in the above industry is yeast. Yeast was one of the first micro-organisms to be used in genetic research. However, in spite of studies in yeast genetics, its applications are few, for three reasons:

(a) Industries already have the desired strains (from trial and error);

(b) New genetic strains are not easily bred; they are incompatible for mating and their genetic characteristics are poorly understood;

(c) Many of the important characteristics of industrial microbes are complex - several genes are responsible for each.

1. Brewing

Due to the changing technologies in the brewing industry and increased sophistication in the molecular genetics of yeast, researchers have achieved new goals, for example, a low-carbohydrate beer for diabetics.

2. Baking

Yeast with new properties for the faster fermentation of dough are now being used. New strains, with improved biological activity, storage stability and yield permit improvements in the baking industry. Previously, most genetic application was in the formation of hybrid yeasts. The newer genetic approach, however, which uses cell fusion opens up possibilities of hybrids developed from strains of yeasts which carry useful genes but cannot mate normally.

3. Winemaking

Genetic research which was carried out with wine yeasts during the past 10 years has achieved the following:

(a) increased alcohol tolerance;

(b) improved sedimentation properties;

(c) improved performance.

Progress in developing strains of yeast with novel properties is hindered by lack of suitable approved systems for using recombinant DNA.

D. Microbial Polysaccharides

Polysaccharides are polymeric sugars which are used to alter or control the physical properties of foods e.g. as thickeners, gelling agents and agents to control ice crystal formation in frozen foods. Since polysaccharides are generally derived from plant sources microbial polysaccharides have had limited use. To be economically viable, a microbial polysaccharide has to be readily available, offer new properties and be considered "safe". To date very few have reached the commercial application level. The only one which is used extensively used commercially is Xanthum gum which is produced from Xanthomonas campestris.

So far, most of the work on polysaccharides has been on one particular strain, but there is growing evidence that they could also be produced from other strains. However, elucidation of the biochemical pathway for the synthesis of a particular microbial polysaccharide as well as an understanding of the systems that control microbial production are necessary before applying genetics.

E. Enzymes

1. Overview

Enzymes are produced for industrial, medical and laboratory use both by fermentation processes (using bacteria, moulds and yeasts) and by extraction from natural tissues. At present less than 50 microbial enzymes are of industrial importance but patents have been given for more than 1,000. This suggests that it may be easier to discover new enzymes than to find a profitable market for them. Most enzymes are used in the detergent industry and the food processing industry especially for processing starch.

2. Food Processing Industry

If biotechnology is applied to the fermentation processes, a larger number of enzymes will be made more available. Furthermore, genetic engineering can open up commercial possibilities in the food industry. Consider, for example, the enzyme pullulanase which degrades pullulan, a polysaccharide, to maltose or high-maltose syrups, which enhance the colour and brilliance of jams and jellies. Additionally, they also reduce the off-colour development produced by heat in sweets and

prevent sandiness in ice creams by inhibiting sugar crystallisation. Maltose is also the least water-absorbent of the maltose sugars and despite being less sweet than glucose it has a more acceptable taste. Additionally, it is fermentable, nonviscous, easily soluble and does not readily crystallise.

Pullulanase can also break down another carbohydrate, amylopectin, to produce high amylose starches. These starches are used in industry as quick-setting, structurally stable gels, as binders for strong transparent films and as coatings. Their acetate derivatives are added to textile finishes, sizing adhesives and binders. In food, amylose starches thicken and give texture to sweets and sauces, reduce fat in fried foods and stabilize the protein, nutrients, colour and flavour in reconstituted foods e.g. meat analogues.

In view of the current shortages of petroleum-derived plastics and the need for a bio-degradable replacement, amylose's ability to form plastic-like wraps may provide its largest industrial market - but that market has not yet been developed.

If applications for the products made by pullulanase can be developed, genetic engineering can be used to insert this enzyme into industrially useful organisms and to increase its production. However, since the food processing industry can only use enzymes that are obtained from sources approved for food use, and since the chief source of pullulanese is a pathogenic bacterium, Klebsiella aerogenes, significant efforts have not been made to apply genetics to improve production or quality. Perhaps genetic engineering could transfer the pullulanase trait from Klebsiella aerogenes to a micro-organism which is approved for food use.

3. Sweeteners, Flavours and Fragrances

Biotechnology has had a marked impact on the sweetener industry. Due to the availability of the enzymes glucose, isomerase, invertase and amylase, the production of high fructose corn sweeteners (HFCS) has been profitable. For example, the Coca Cola Company uses five per cent fructose.

Although it is unlikely that sucrose will ever be made by micro-organisms, the microbial production of low calorie sweeteners is a distinct possibility. Three low calorie sugars, aspartame, monellin, and thaumatin have been studied.

F. General View

An industry-wide impact is not expected due to the following three reasons:

(a) The basic genetic knowledge of characteristics that could improve food has not been adequately developed;

(b) The food processing industry is cautious in its expenditures on R+D for important processes; generally, they allocate half as much as the more technically sophisticated industries;

(c) The products from the new microbial sources must satisfy the FDA safety regulations; it may be possible to reduce the amount of testing by transferring the gene into micro-organisms that already meet FDA standards.

However, it is expected that the application of genetic technologies will accelerate. The aim is to draw technically sophisticated companies into the business.

V. MINERAL LEACHING AND RECOVERY

Most genetically engineered micro-organisms are designed for contained facilities. However, some are examined for usefulness in the open environment for purposes like mineral leaching and recovery, oil recovery and pollution control. All three applications are characterised by:

(a) use of large volumes of micro-organisms;
(b) less control over the behaviour and fate of micro-organisms;
(c) possibility of ecological disruption;
(d) less basic R+D.

All micro-organisms interact with metals. Two interactions which are of potential economic and industrial interest are leaching metals from their ores and concentrating metals from wastes or dilute mixtures. The former would allow the extraction of metals from large quantities of low grade ores while the latter would provide a method for recycling precious metals and controlling pollution caused by toxic metals.

A. Microbial Leaching

When metals in ores are made soluble by bacterial action it is termed microbial or bacterial leaching. Historically, the process has been shown to be effective.

Leaching begins with the circulation of water through large quantities of ore. The bacteria, which are naturally associated with the rocks, then cause the metals to be leached. This is done by one of two general mechanisms - either the bacteria act directly on the ore to extract the metal or they produce substances (e.g. ferric iron and sulphuric acid) which then extract the metal. It has been shown that adding acid is not as efficient as using live bacteria. In fact, empirical evidence indicates that some of the bacteria involved in mineral leaching bind strongly to those minerals.

The application of the leaching process to uranium mining has aroused considerable interest due to the possibility of *in situ* mining. It has also been suggested that extending this practice to other mines would be environmentally beneficial due to the minimal disruption of land surfaces. Although the process is slower than the current technology, it is cheaper and simpler.

B. Applied Genetics in Strain Improvement

Thiobacillus ferrooxidans is the bacterium most studied for its leaching properties. Very little is known about the mechanism concerning the leaching ability in the bacteria. This is because very little information exists in two areas: the chemistry of interaction between the bacteria and the rock surface, and the genetic structure of the micro-organism.

Due to the lack of genetic and biochemical information about these bacteria, the application of genetic technologies to mineral leaching is still speculative. Progress is slow.

Even when scientific knowledge is gathered, two obstacles to the use of genetically-engineered micro-organisms will remain:

(a) The need to develop engineering systems on a large enough scale to exploit biological activities. A constant interchange between geneticists, geologists, chemists, engineers etc. must take place - i.e. each must understand the needs and problems of the other. The answer lies in forming an interdisciplinary group.

(b) This obstacle is environmental. Introducing large numbers of genetically engineered micro-organisms into the environment raises questions of ecological disruption, as well as liability, if damage occurs to the environment or human health.

C. Metal Recovery

The use of micro-organisms to recover metals from dilute solutions has two goals, namely to recover metals as part of a recycling process and to eliminate any metal that may be a pollutant. The process utilizes the ability of the micro-organisms to bind metals to their surfaces and then concentrate them internally.

Studies have shown that micro-organisms can be used to remove metals from industrial effluents. This is particularly useful for low concentrations (10 to 100 ppm) where non-biological methods are uneconomical.

The economic competitiveness of the biological methods have still to be proved; the genetic improvements, however, have been tried only recently. The cost of producing the micro-organisms has been a major contraint; if this can be reduced, the method might be useful.

Like other biological systems, genetic engineering may increase the efficiency of the extraction process. However, the capability to select cells with the genetic ability to accumulate large amounts of specific, desired metals will be a significant stride in designing a practical system.

VI. OIL RECOVERY

Oil production can be increased by the following three methods:

(a) accelerating exploration for new oil fields;
(b) mining oil shale and coal and converting them into liquids;
(c) developing new methods for recovering oil from existing reservoirs.

There are three methods of oil recovery - primary, secondary and tertiary. In primary methods, physical expansion is used to drive the oil out of the formation. In secondary methods, a fluid (water, natural gas) is injected into the reservoir to force the oil to the well. The tertiary method (also known as enhanced oil recovery (EOR)) is relatively new. It uses chemical and physical methods to increase the mobility of the oil - thus facilitating other forces to drive it out of the ground. It is here that genetic engineering could be used - e.g. a micro-organism could be used to help bring out the oil. The tertiary method is good for oil in sandstone and limestone reservoirs as well as for sands and oil shale.

A. Enhanced Oil Recovery

There are four EOR processes - all aimed at dislodging crude oil from its natural (geological) setting.

1. Thermal

The oil reservoir is heated which leads to a decrease in the viscosity of the oil. Using the pressure of the air that is introduced, combustion occurs which in turn forces the petroleum to the producing well. Thermal processes cannot be improved using genetic technologies.

2. Miscible Processes

This process injects chemicals which stand with the crude oil to form mixtures that flow more readily. The chemicals used are alcohols, carbon dioxide, petroleum hydrocarbons (e.g. propane, butane) and petroleum gases. A fluid (usually water) is used to push the slug of these chemicals through the reservoir to mix with the crude oil and move to the surface.

3. Alkaline Flooding, Polymer Flooding and Combined Surfactant/Polymer Flooding

(a) Alkaline Flooding - sodium hydroxide, sodium carbonate or other alkaline materials are used to enhance the oil flow. Neither natural nor genetically engineered micro-organisms are considered useful here.

(b) Polymer Flooding - this is a recent and successful method which depends on the ability of polymers to increase the viscosity of water. Instead of altering the characteristics of crude oil, it aims to make the injected water more capable of displacing it.

(c) Combined - here a surfactant (detergent-like material) is used to loosen the oil from the surrounding rocks, while the water that contains a polymer (to increase its viscosity) is used to drive the oil from the reservoir.

4. Other EOR Methods

This includes many novel possibilities e.g. the injection of live micro-organisms into a reservoir - these may produce any of the chemicals, from surfactants and polymers to carbon dioxide, used in the miscible and flooding processes.

B. Microbial Production of Chemicals used in EOR

EOR methods which use chemicals tend to be costly due to the cost of chemicals. However, potentially useful polymers were found in the early 1960s and have been used since for oil recovery e.g. polyacrylamide and xanthan gum both of which can increase the viscosity of water in concentrations as low as one part per thousand. Xanthan gum, which can be made by micro-organisms, has good viscous properties but it is expensive to make. Furthermore, if it is not exceptionally pure, it can plug reservoir pores. The fluid has to be filtered carefully to remove bacterial debris before it is injected.

However, it is possible to genetically engineer a micro-organism which can overcome many difficulties; e g. polysaccharides (polymeric sugars), with improved properties, could be obtained by microbial fermentation and used effectively.

Biological processes have disadvantages too, mainly in the costs of appropriate raw materials and the need for large quantities of solvents. Recent efforts to find cheaper raw materials e.g. sugar beet pulp and starch show promise. It is possible to overcome the problem of precipitating and concentrating the polymers by producing them in situ (on the site). Micro-organisms can also produce butyl and propyl alcohols that can be used as co-surfactants in EOR.

The lack of technical and economic data together with insufficient field experiments makes the situation uncertain. Each oil field has its own set of conditions and laboratory tests are insufficient to determine field conditions.

C. Use of Micro-organisms In Situ

If micro-organisms could be injected directly into wells then the chemicals could be produced in situ (by the micro-organisms). However, geophysical and geochemical conditions in the reservoirs seldom favour the growth of micro-organisms. The problems are: high temperature, presence of sulphur and sodium chloride, low oxygen and water, extremes of pH and engineering hurdles.

The micro-organisms must be fed and the micro-environment must be carefully adjusted to their needs at thousands of feet. However, information from geomicrobiology suggests that this approach is worth pursuing, e.g. injection of Bacillus or Clostridium species together with a water suspended mixture of fermentable raw materials (cattle feed molasses and mineral nutrients) has produced plenty of carbon dioxide, methane, and some nitrogen in the reservoirs. The carbon dioxide made the crude less viscious and the other gases aided in redressing the reservoir pressure. Furthermore, large amounts of organic acids formed additional carbon dioxide through reactions with carbonate minerals. The production of microbial surfactants further aided this process.

Although it was formally believed that reservoir pressure hindered the growth of micro-organisms, recent data shows this is not so.

However, the micro-organism must be selected for increased salt and pH tolerance.

D. EOR and Genetic Engineering

The current research approach is a two phase process. The initial one is to find a micro-organism which can function in an oil reservoir environment with as many of the necessary characteristics as possible. The subsequent one is to alter the micro-organism genetically to enhance its overall capacity.

The genetic engineering of micro-organisms to produce chemicals which can be used in EOR has been successful, whereas the genetic engineering of micro-organisms to be used in situ has been less successful

E. Constraints to Applying Genetic Engineering Technology in EOR

The genetic data base for micro-organisms that produce useful polysaccharides is weak and thus theoretical studies cannot be done just yet.

The biochemical data base for characteristics of both the micro-organisms and their products is also lacking. There is potential, however, for chemical reactions carried out by microbes - this has to be further investigated. Furthermore, a classification and characterisation system for the micro-organisms must be devised.

The physical data base for oil reservoirs is limited due to the uniqueness of each reservoir. No universal micro-organism or method of oil recovery will be found. This is further complicated by the lack of sufficient physical, chemical and biological information about reservoirs - and without this it is not possible to rationalise a constructive genetic scheme for strains. The conditions have to be known.

There are three institutional objectives. Primarily since most of the research results are confidential, the number of available publications is limited.

Secondly, neither the private nor public sector is enthusiastic about the potential use of micro-organisms in EOR. The biological approach has only recently been considered. Thirdly, any efforts to use micro-organisms must be multidisciplinary. Geologists, microbiologists, chemists and engineers must interact.

The environmental and legal concerns have also restricted progress. Since microbial EOR methods require plenty of fresh water, they could compete with municipal and agricultural uses. The immediate environmental and legal concerns stem from the potential risk associated by releasing micro-organisms into the environment. When the organisms naturally cause disease or environmental disruption, the use is limited. When they do not, the risk is always there. Caution has to be exercised at all times.

F. Genetic Engineering for Other Aspects of Oil Recovery and Treatment

Two other aspects of microbial physiology are: the microbial production of oil muds or drill lubricants and the post recovery microbial treatment of oil. Drilling muds are suspensions of clay and other materials. These lubricate the drill as well as counter-balance the upward pressure of the oil. Microbially produced polysaccharides are being developed for this purpose.

The post recovery microbial treatment of oil concerns the ability of micro-organisms to remove undesirable constituents from the crude oil. Recently, three microbial systems have been developed to help remove aromatic sulphur-containing materials - a major impurity.

G. General View of Genetic Engineering in Mining and Oil Recovery

The main thrust is in developing genetically engineered micro-organisms in either mining or oil recovery. Both require land and materials such as fluids and micro-organisms in large quantities. Laboratory test results cannot be automatically extrapolated to industrial applications. Furthermore, the variables in the natural environment cannot be envisaged. However, due to the potential value of the products in these areas research and development will continue.

VII. POLLUTION CONTROL

Micro-organisms have been used for years to degrade and detoxify human sewage. Now, micro-organisms are used to tackle pollution problems caused by industrial toxic wastes.

Pollution problems have been categorised into two areas - those present for a long time in the biosphere (e.g. hydrocarbons found in the petroleum industry and in human and animal wastes) and those which are the result of human inventiveness (e.g. pesticides). Chemicals of both sorts (due to various reasons) often appear in places where they are hazardous to humans or the environment.

Microbes can control pollution in two ways: either by enhancing the growth and activity of microbes already present at or near the site of pollution, or by adding more and/or new microbes to the site. Genetic engineering cannot aid the former. However, genetic engineering could make a significant contribution to the latter.

Some companies have already marketed microbes which could be added to the site. In addition, certain microbes are geared for specific problems, e.g. oil, sewage, etc.

The cities are cautious about adding bacteria to large municipal sewarage systems, but the view that bacteria may be useful in smaller installations and for specific problems has gained support.

The resistance to genetically engineered bacteria is not universal. Many industrial wastes are oxidised to non-toxic chemicals by biological treatment in aerated lagoons. The process depends on the presence of microbes in lagoons - the microbes that grow best on the waste eventually dominate the microbial population of the lagoon. Three companies now sell bacteria which they claim are more efficient than the indigenous strains found in the lagoon.

There exists, however, a disagreement regarding the value of adding microbes to decontaminate soils or waters. One view contends that serious spills often sterilise soils and adding microbes is necessary for any biodegradation, while the other argues that encouraging indigenous microbes is more likely to succeed as they are accustomed to the spill environment.

Thus, although genetics has not been much applied to pollution control, the potential is strong. The constraints are:-

(a) health, economic and environmental damage;

(b) added organisms are unlikely to be a significant improvement;

(c) selling microbes rather than products or processes is unlikely to be profitable:

The factors which have discouraged development are:-

(a) no convincing evidence that microbes could remove or degrade an intractable pollutant;

(b) the research required to produce marked improvements is inhibited.

In order to overcome this inhibition, governments need to support the research, buy the microbes and to provide for protection against liability suits. Such a stand would help protect health and the environment from the toxic effects of pollutants.

ANNEX

TIME HORIZONS FOR COMMERCIALIZATION OF GENETICALLY ENGINEERED STRAINS

	Five years	Current market value ($ million)
Amino acids (arginine, aspartate, cysteine, glutamate, lysine, phenylalanine, threonine, tryptophan)		1 409
Enzymes (α-amylase, amyloglucosidase, asparaginase, [1] *Bacillus* protease, glucose isomerase, glucose oxidase, papain, pepsin, rennin, tyrosine, [1] urokinase)		218
Peptide hormones (adrenocorticotropic hormone (ACTH), bovine growth hormone, [2] endorphins, [1] enkephalins, [1] glucagon [1], human growth hormone, insulin, vasopressin [1])		264
Viral antigens (avian leukemia, avian myeloblastosis, Epstein-Barr, hepatitis, herpes, hoof and mouth, Rous sarcoma, rubella, varicella)		n.a.
Short peptides, nucleotides and miscellaneous proteins (aspartame, glycine-histidine-lysine, interferon, human serum albumin)		304
Pesticides (microbial)		25
Aliphatics (ethylene glycol, ethylene oxide, glycerol, itaconic acid)		1 225

1/ Market information not available

2/ No market value at present

	Current market value ($ million)
Aromatics (aspirin, p-acetaminophenol)	99
Total	3 544

Ten years

Amino acids (methionine)	294
Vitamins (nicotinic acid, riboflavin, vitamin B_{12}, vitamin C, vitamin D)	561
Enzymes (ethanol dehydrogenase, hydrogenase)	n.a.
Corticoids (cortisone prednisone, prednisolone aldosterone)	306
Androgens (testosterone)	11
Estrogens (estradiol)	60
Peptide hormones (ovine growth hormone, porcine growth hormone)	n.a.
Viral antigens (influenza)	n.a.
Short peptides, nucleotides and miscellaneous proteins (5^1-IMP, 5^1-GMP, monoclonal antibodies)	72
Antibiotics (penicillins, tetracyclines, cephalosporins, erythromycins)	2 560
Pesticides (aromatics)	75

	Current market value ($ million)
Aliphatics (acetic acid, acrylic acid, adipic acid, ethanolamine, isobutylene, methane, pentaerythritol, propionic acid, propylene glycol, sorbitol)	12 904
Aromatics (aniline, benzoic acid, cresols, phenol)	663
Total	17 506

Fifteen years

Vitamins (vitamin E)	106
Viral antigens (reoviruses)	n.a.
Gene preparations (sickle cell anaemia)	n.a.
Aromatics (pthalic anhydride)	259
Inorganics (ammonia, hydrogen)	2 681
Total	3 046

Twenty years

Gene preparations (hemophilias, thallasemias)	n.a.
Aliphatics (Bis (2-ethylhexyl) adipate), critronellal, citronellol, geraniol, linalool, linalyl acetate, nerol, α-terpineol, α-terpinyl acetate)	57

	Current market value ($ million)
Aromatics (cinnamaldehyde, diisodecyl phthalate, diocytl phthalate)	231
Total	288

	Current market value ($ million)
Five years	3 544
Ten years	17 506
Fifteen years	3 046
Twenty years	288
Total	$24 384

Note: Except for aromatics and aliphatics, all market data represent worldwide estimates. Market data for aromatics and aliphatics are restricted to the United States.