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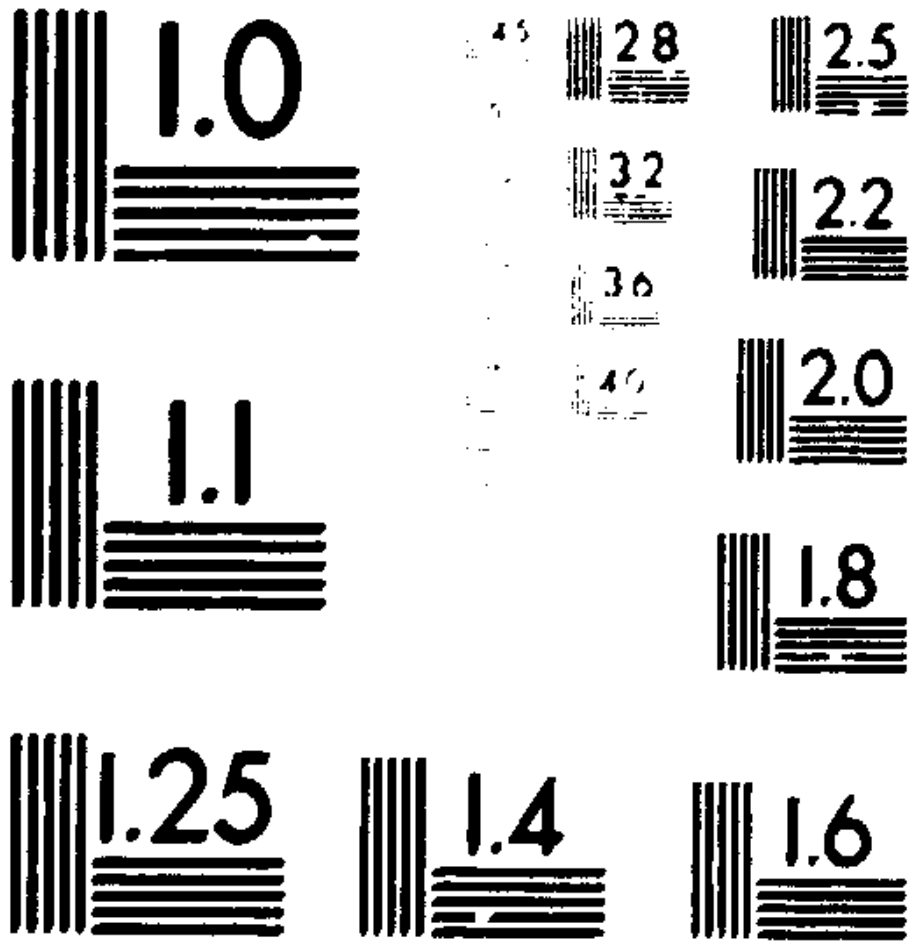

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Genetic Engineering and Biotechnology Monitor

TRENDS IN WORLD BIOTECHNOLOGY

A review and analysis of advances in technology and industrial development during 1982-1983 with projections to the future

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* The views expressed in this document are those of the author and do not necessarily reflect the views of UNIDO.

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INTRODUCTION

Biotechnology is a term that was coined during the late 1970s when recent advances in molecular and cell biology, particularly the development of certain techniques, prompted the investment of large sums of money in new industrial ventures to exploit these advances. This definition of biotechnology encompasses all industrial applications of recombinant DNA methods which allow "new" or "foreign" genetic material to be incorporated and expressed in a suitable host cell, such as a bacterium or cultured animal cell - "genetic engineering" in popular terms. It also includes the applications of advances in immunology - especially techniques that allow a single homogeneous type of antibody to be produced in large quantities (monoclonal antibodies) - to a variety of problems from the accurate diagnosis of diseases to the construction of novel cancer therapeutics. The use of these and related methods in human and veterinary medicine, agriculture, and industrial chemistry, biochemistry and microbiology comprise the modern definition of biotechnology.

In a broader sense, biotechnology, or industrial processes based upon the application of fundamental biological knowledge, particularly microbiology, has been with us for many decades. That is, the selection and improvement of strains of microbes for the efficient, large-scale production of antibiotics has been carried out for more than forty years. Large scale fermentation of bacteria and fungi has been in use for many decades for the production of a wide variety of products. The manufacture of beer as an industrial process can certainly be considered one of the earliest examples of biotechnology. In many ways, modern biotechnology is very similar to a number of these earlier expressions of applied microbiology. We have merely developed highly advanced ways for the selective manipulation of the genetics of not only micro-organisms but of the cells of higher plants and animals as well.

As we enter 1984, biotechnology has become well established as the newest "high technology" industry. Most of the industrial development to date has resulted from the investment of private capital to form well over 200 small (under 500 employees) entrepreneurial companies, and from new programmes initiated by literally hundreds of large corporations. In some instances, countries wishing to promote biotechnology within their boundaries, have set aside significant sums to aid in the establishment of a domestic industry.

Most of this activity has been confined to the most economically advanced nations (United States, Japan and those of Western Europe). However, there are at present many initiatives to establish modern biotechnology in a number of developing countries, along with the advanced research capabilities upon which the industry is based. Several mechanisms are being explored to accomplish this goal.

The directions which the present biotechnology industry have taken are determined largely by the economics of potential products and their anticipated markets. That is, there has been investment in the development of products for

which a demand exists, or probably would exist, from consumers able to pay for those products. Thus, there has been relatively little concern for products of interest primarily to developing countries, even though the demand may be great, because they cannot pay enough. In addition, stringent regulatory requirements, such as those that must be met in most countries for any human pharmaceuticals or biologicals, add considerable costs and years to the development of such products, creating a disincentive to pursue any but those products deemed to be the most lucrative. Thus many companies choose to develop vaccines for animal, rather than human diseases. Nor is there development in those areas where the same or competing products can be produced more economically by conventional means. For example, the 1984 world price of petroleum is a disincentive to apply biotechnology to the production of fuels or alternative energy sources.

From a technical perspective, the rate of advancement in biotechnology in its short history as a coherent industry has been spectacular. In part, this certainly reflects the fact that advances in the underlying basic biological sciences in the past fifteen years have been similarly spectacular. Many of the same leading scientists who contributed some of the foremost achievements in molecular biology, genetics and immunology are actively involved in current activities of the biotechnology industry. While it is not yet clear what the industry will have achieved in a decade from now, it is certain that contributions by biotechnology will in many respects significantly transform the ways in which we live.

None the less biotechnology is an industry in its early youth, just entering its adolescence. There are relatively few products available to consumers in comparison to the large expenditures for research and development. Many of the existing independent organizations were founded by scientists with relatively little business experience. As a result, a number of these companies are today struggling with the problem of finding effective management and a research and development strategy conducive to survival in a highly competitive commercial environment.

This review and analysis, therefore, provides a glimpse of a youthful industry in the process of undergoing rapid evolution. The criteria for survival have not yet been clearly defined, so it is difficult to identify the survivors, or in what form they will appear when the rate of change diminishes. Neither is it clear what differences will ultimately emerge between the industry evolving in the Third World and the highly commercialized, economically driven industry of the leading industrialized countries.

However, by examining the trends of the biotechnology industry over the past two years, both with respect to its technological advances and world industrial development, it is possible to identify those directions in which biotechnology is heading, and project the course of its future progress. In doing so, one can also identify certain problems which are likely to prove troublesome and will have to be dealt with by both the industrial entrepreneurs and the architects of national industrial policies.

HISTORICAL PERSPECTIVE

The seeds of the rapidly growing biotechnology industry were sown in the early 1970s with the development of methods for the splicing of discrete deoxyribonucleic acid segments (DNA) in a functional manner into the DNA of a different, perhaps unrelated, organism. In this way, the gene coding for a rare human protein of medical importance - a hormone or a peptide releasing factor for example - could, in principle, be spliced into the DNA of a common bacterium. This bacterium could, in turn, be grown quickly and in large quantities to produce an unlimited supply of the rare and expensive material.

This was the scenario described by the scientists who wished to impress upon the public the enormous potential of these recombinant DNA methods. In the beginning, such statements were at least partially defensive, in the face of some strident criticism that gene splicing was accompanied by potential hazards and, therefore, should be carried out only under stringent safety precautions, if at all. But it was also such a scenario that inspired the boom of entrepreneurship and investment in the development of an industry that could exploit the marvels of gene splicing. 1/

However, as the would-be entrepreneurs were planning how to go about establishing industrial organizations, several more significant research developments made the concept of applied modern biology even more attractive. Cell fusion techniques, leading to the production of monoclonal antibodies, were as important as gene splicing in opening new areas for industrialization. 2/ Methods for isolating genes, 3/ for determining the base sequence of DNA, 4/ and for synthesizing polynucleotides of defined base sequence, 5/ all helped to greatly increase the scientists control over the genetic modifications of medically and industrially important organisms. Techniques for the culture of plant cells and for the regeneration of differentiated plants, along with attempts to introduce new genes into plant cells, promised to bring the tools of genetic engineering to agriculture, and the continuing improvement of ways to introduce new genes into animal cells has greatly expanded the possibilities for producing complex human gene products as well as the promise of improvement of livestock strains.

By 1977, there were a handful of independent companies in the United States (Genentech, Genex, Cetus, Bethesda Research Laboratories) and one in Switzerland (Biogen) whose primary object was to capitalize on these new techniques. The large pharmaceutical and chemical concerns in the United States and Europe all clearly had a stake in the future of biotechnology, and were well represented in public discussions on the future of the new technology. However, it was the new small companies, with the aid of the eminent professors who were their founders and advisors, that took the early lead.

For the next five years, the entrepreneurial industry expanded greatly in the United States, with more than 150 independent companies in existence by 1982. In Japan, the Ministry of International Trade and Industry (MITI) identified biotechnology as a national priority, implementing policies providing incentives for existing companies to begin to invest heavily in new biotechnology programmes. Most of the biotechnology activity in Europe was confined to new programmes within the larger pharmaceutical and chemical companies, 6/ but the development of biotechnology was sufficiently slow to prompt the concerns of several governments. France and the United Kingdom each provided government funds to stimulate the formation of new industrial concerns devoted exclusively to biotechnology (Transgene and Celltech, respectively).

In the autumn of 1980, the US company Genentech offered stock for sale to the public. The extraordinary demand for shares by investors indicated the great expectations of the investing public in the future of biotechnology. Cetus followed Genentech's example with a record stock sale in March 1981. Other companies also engaged in public stock offerings, although the glamour began to fade by late 1981. 1/ The impatience of the investment community then led to the castigation of the fledgling biotechnology industry in the press 7/ for not delivering the wonderful products it had promised and making its investors rich. The misleading publicity of companies wanting to raise capital and the hopes of the investors had created a false picture of the capacity of the new industry to translate science into technology in what would have been an unprecedented short time. In fact, it requires years to carry out the development of an economical, high yielding process to produce virtually any substance, even after the basic methodology has been demonstrated in the laboratory.

The large corporations which had been slow to exploit the promise of biotechnology in the early years, now began to lose their inhibitions and committed substantial sums of money to research and development in these exciting new areas. In many cases they preferred to invest in the independent companies, thereby forming many partnerships and co-operative research agreements. Some, however, began to develop substantial programmes of their own. Most of this activity was confined, as expected, to the large pharmaceutical and chemical companies. DuPont, for example, announced that it was committing US$100 million to new research and development in the life sciences. A number of petroleum refiners (e.g., Shell, Arco, Standard Oil) were also making major commitments to biotechnology. 6/

Some of the excitement over biotechnology that attracted huge sums of investment capital in 1981 was also experienced by industrial planners in developing countries and in international organizations faced with the problems of world economic development. Biotechnology clearly offers the potential to help solve a number of the major problems that beset the developing nations, particularly those pertaining to human and animal health, such as vaccines, shortage of food and shortfalls in energy.

Some United Nations organizations began to address different aspects of the extension of biotechnology to the problems of developing countries. The World Health Organization (WHO) funded some research programmes utilizing the new biological techniques, including a project to develop a vaccine for malaria. The United Nations Industrial Development Organization (UNIDO) began discussions and consultations with a number of countries to explore the possibility of establishing an international research, development and training centre devoted to the promotion of biotechnology in the Third World. 8/ The World Bank began to examine long-term loans to developing countries for projects involving biotechnology. Overall, however, there was very little activity outside the major industrialized countries prior to 1982. Existing national and international programmes were focused much more on the use of conventional techniques in plant breeding and fermentation. Only in some of the universities in Third World countries were programmes begun in research involving genetic manipulation and some other of the new techniques. In most cases, these were initiated by scientists who had been trained in leading laboratories abroad. These activities, however, represent an important beginning for the establishment of a self-sustaining biotechnology industry in developing countries.

TECHNOLOGICAL ADVANCES 1982-1983

(a) Basic science and methodology

The two-year period 1982-1983 was one of continued rapid advances in the development and refinement of basic techniques, as well as their application to a number of practical goals. Of particular relevance to biotechnology are (1) a continued elucidation of the process of carcinogenesis and the genetics of cancer, 9/ (2) better understanding of the regulation of the immune system, 10/ (3) improvement of methods for the stable introduction of new genes into mammalian cells, 11/ (4) improvement of techniques for culturing and regenerating plant tissue, (5) the development of methods for introducing new genes into plant cells, 12/ and (6) the development of bacterial excretion vectors for the more economical production of many cloned gene products. 13/

One of the foremost challenges in molecular biology has been to understand the control of gene expression in mammalian cells. In the late 1970s, recombinant DNA methods revealed that most genes in mammalian cells were discontinuous - that is, the coding regions of DNA were interrupted by several rather long stretches of DNA which at first appeared to have no function. 14/ The entire region of DNA comprising a gene is transcribed into RNA, which is then cut and spliced to yield a messenger RNA molecule containing only the coding regions. The function of these "silent" regions and of the DNA immediately preceding the coding regions has remained a mystery, although some postulate a role for these regions in the control of genetic expression and in evolution. 15/ Recent studies on the function of Z-DNA, a newly discovered helical conformation of DNA, suggest that some aspects of the control of gene expression in mammals lie in these conformational properties. 16/ A thorough understanding of mammalian gene expression will be of great value to the genetic engineers' efforts to produce exact copies of a number of complex human proteins using bacterial cloning vehicles (e.g., antibodies, glycosolated proteins, immunoregulators).

Improvements in certain types of instrumentation have also been of great value to the biotechnology industry. Perhaps the most useful method to be automated is that for synthesizing polynucleotides of specified base sequence. During the past two years, improvements in these "gene machines" 5/ have greatly eased the burden of constructing DNA probes for the isolation of genes, or for modifying the base sequence of a structural gene to alter the properties of the gene product.

(b) Human medicine

The initial focus of most industrial genetic engineering activities was on the production of rare human proteins using bacterial cloning vehicles. It has perhaps been the most straightforward and therefore successful activity in the biotechnology industry to date, and will continue to be so as long as the protein produced is clearly a useful substance. At the beginning of 1982, bacterially produced human insulin was being readied for market, 17/ and human growth hormone had been approved for clinical trials. 18/

(i) Cancer therapeutics

However not all of the targets of bacterial cloning and expression have been substances of known value. The darling of the late 1970s, interferon, which had prompted much hope that a cure for cancer would be found, was one of the early substances to receive attention by the fledgling biotechnology industry. 19/ In the early 1980s, several natural interferons were being tested as cancer therapeutics. 20/ The cloning and expression of all three types of human interferon (alpha, beta and gamma) was receiving attention from at least 25 companies, with several others sponsoring research projects in university laboratories. 21/ During 1982 and 1983, improvements were made in the synthesis and yield of these "synthetic" human interferons. Problems were encountered in making a product that had the same spatial conformation as the natural product and that had comparable specific activity in in-vitro anti-viral assays.

One American company (Cetus) substituted a serine for one of the three cysteine residues of human beta interferon in order to ensure the proper position of the disulfide bond, with a corresponding increase in activity. 22/ Others (Genentech, Biogen and the Japanese firms Shionogi and Kyowa Hakko Kyogo, among others) achieved the production of cloned gamma interferon. These and other forms of interferon are currently undergoing clinical trials as cancer therapeutics. 23/ Thus far, however, the clinical results of those interferons tested have fallen far short of the initial (and perhaps unjustfied) expectations. While some improvement has been seen for a few types of cancer, such as leukaemia, they are scarcely magic bullets. It may, however, be useful in conjunction with conventional therapies. It should not be forgotten that interferon was first discovered as an agent that was involved in curtailing viral infection, a property which gives it its name. It may yet prove far more useful as an anti-viral agent, in keeping with its natural function, than as a cancer therapeutic. 24/

The interferons were the first class of immunomodulators receiving attention from the biotechnology industry. Of perhaps greater current interest are the lymphokines, proteins that regulate the proliferation and activity of T-lymphocytes (cells which play a key role in fighting infectious diseases and probably cancer). 25/ One of these, interleukin-2, has been cloned and expressed by a number of research groups and is now receiving intense investigation as a cancer therapeutic because of its ability to stimulate the so-called natural killer (NK) T-cells. These cells appear to be of importance in the body's natural defence against tumor cells, which they recognize as alien, and subsequently attack and destroy. The commercial competition to produce, test and market interleukin-2 is intense, involving many companies in the United States, Japan and Europe, even though its value as a general therapeutic against cancer is uncertain. That is, there is evidence that the T-cell population one wishes to enhance must contain recognition elements specific for markers on the tumor cells, making a therapeutic regimen far more complex than the simple injection of an immune modulator into the blood stream of a patient. A number of the other lymphokines are also being studied to elucidate their roles in immune regulation and as possible new products for the treatment of cancer and other diseases. 26/

The past two years have seen great gains in the understanding of cancer. The elucidation of "oncogenes" - genes in which a simple mutation, or a rearrangement of the position of the gene on the chromosome, seems to be associated with the transformation of a normal cell into a cancerous one - has at least provided the beginning of our understanding of the process of carcinogenesis. 27/ Additional clarification of the process by which cancer

cells metastasize and undergo their own rapid evolution and diversification has, unhappily, given us a better idea of the formidable problem facing those seeking an effective therapeutic agent. 28/ Even if the primary tumor can be treated and destroyed, once malignant cells have migrated to other sites and assumed properties different from the parent tumor even specific immunotherapies may be too difficult to develop, even on an individual patient basis.

Nevertheless, the investigation of naturally occurring substances of importance in the immune system has led to a considerably better understanding of the body's natural defence mechanisms than we had even two years ago. It is likely that therapies for cancer and auto-immune diseases will eventually be forthcoming from these studies, although the long hoped for big "breakthrough" of an all purpose effective treatment for cancer may remain forever elusive.

The other area of immunology that has been an ideal subject of exploitation has, of course, been that dealing with antibodies. Already by 1980, there were several companies in the United States developing monoclonal antibody technology for use both in diagnostics and therapy for a variety of conditions. 29/ By the beginning of 1984, there were a number of diagnostic products on the market using monoclonal antibodies. 30/

One use of homogenous antibodies that is receiving a great deal of attention is the construction of immunotoxins - molecules consisting of a monoclonal antibody, or the active portion thereof, linked to the active chain of a biological toxin. Most protein toxins (diphtheria, ricin, botulin) consist of a protein chain that bind to sites on cell surfaces linked to a chain that enters and kills the cell, usually through an enzymatic activity. In an immunotoxin, the portion of the toxin that binds to the cells is replaced by the antibody molecule.

The application of immunotoxins of most interest is as a cancer therapeutic, assuming that cancer cells have unique, accessible antigens that can be isolated and used to make specific monoclonal antibodies. If the antibodies specific to the tumor cells were linked to a powerful cytotoxin, then presumably this substance would kill only the cancer cells, leaving the normal cells intact. 31/ While there has been some success in selectively destroying cultured tumor cells, there are a number of difficult practical problems to be overcome in designing an effective immunotoxin therapy, especially concerning the delivery of the agent to the site of the tumor. Solid tissue tumors present the most difficulty. Research is thus being directed towards the design of immunotoxin molecules that are smaller and effectively partition the blood stream from the tissues. Molecular engineering methods, discussed later in this report, may be very useful in solving the problems of access to the tumor site, resistance to the body's own defense mechanisms, degradation, etc. However, the antigenic diversity of tumors, both among patients and within the same patient, may prove to be an insurmountable barrier to any generic therapy based on antibody technology. 28/

(ii) Infectious diseases - vaccines

The design and production of safe vaccines is an obvious application of gene splicing technology. First, the most antigenically active portions of the viral coat protein or the bacterial cell surface proteins are identified. The DNA for these regions is then isolated and cloned, each in a separate cloning vehicle. The purified gene products constitute the vaccine, the most effective generally being those using several different antigenic components.

Perhaps ironically, the first recombinant DNA vaccines, which made their debut during 1982-1983, were for animal diseases. Several companies now market vaccines for scours, a bacterial diarrhoeal disease afflicting newborn calves and piglets (Intervet, Cetus/Norden, Akza), but further research is required to develop more effective agents. A cloned vaccine for foot-and-mouth disease, the world market for which is greater than any other human or animal vaccine, is being tested and should be available soon. 32/ There are, however, several antigenic strains of the disease throughout the world. Effective prevention will require vaccines against each of these forms.

Relatively little of the great potential of genetic manipulation techniques for making vaccines is being directed toward the development of human vaccines. There are several reasons for this, all of them economic. In the economically developed countries where most of the existing commercial biotechnology exists, all pharmaceutical substances intended for human use must undergo rigorous testing for safety and efficacy, procedures and clinical trials that require many years and millions of dollars for each substance tested. Animal drugs and vaccines require far less lengthy and costly testing in order to be approved for marketing. Thus, with limited resources for vaccine development and a significant demand for the control of certain animal diseases (including even those which afflict pet cats and dogs), the biotechnology companies generally find animal vaccines make more economic sense. The major infectious diseases that used to be serious health problems in industrial countries (e.g., smallpox, polio, diphtheria, measles) have been brought under control by improved living conditions and sanitation, and by conventional vaccines. The possible exception is hepatitis B, which is of high enough incidence both in developed and developing countries to justify some investment in vaccine development. 33/

In spite of the fact that there are many serious infectious diseases of high prevalence in developing countries, especially certain of the tropical and parasitic diseases (e.g., malaria, schistosomiasis, and dengue fever), 34/ neither the afflicted nor the countries in which they live are able or willing to pay enough to the companies of the North and West to develop the appropriate vaccines. In fact, a principal sponsor of research and development in vaccines for tropical diseases is the US Department of Defence, which has contracted with Molecular Genetics, Inc., to develop a vaccine for Rift Valley Fever, and is sponsoring other research to develop vaccines against anthrax and dengue-2 virus. 35/ Clearly, these projects were not begun purely out of humanitarian motives. Thus, an area of great human need, for which biotechnology could be of great value, is being neglected. Possible solutions to this dilemma are discussed elsewhere in this report.

(iii) Diagnostic agents

The greatest advance in recent years that has enabled the design and construction of highly sensitive diagnostic agents for a variety of infectious diseases, some forms of cancer and other disorders producing any unusual substance has, of course, been the development of monoclonal antibody methods. The term "monoclonal" derives from the fact that any single type of antibody molecule is produced by a single clone of B-lymphocytes, or, in the methods used in the laboratory, a single clone of hybridoma cells. Hybridomas result from the fusion of a single B-lymphocyte with a type of cancer cell to create an immortal antibody producing cell line well suited to laboratory and industrial production methods. During 1982-1983, a number of monoclonal antibody diagnostic products were developed and marketed. 30/ In some cases, the pure antibody itself is sufficient for an assay involving the precipitation of an antibody-virus or antibody-cell complex. More sensitive assays involve the

linkage of a dye, a radio-isotope or, more often, an enzyme mediating the conversion of a colourless substance to a coloured one, to the antibody molecule.

The complexities of the human genome are inexorably yielding to the genetic probe techniques that have undergone rapid development in the past two years. Human genes and gene families can be isolated and studied by using either messenger RNA or relatively short segments of homologous DNA as probes, to fish out the desired sequences from the total DNA complement of an individual. Once found, the entire base sequence of these genetic regions can be determined.

Apart from the usefulness of these methods in understanding genetic structure and function, a new class of diagnostic agents has emerged. 36/ Not only can DNA probes be made specific for certain sequences of the DNA of infectious organisms, but they can be constructed to detect the presence of hereditary diseases even before birth through foetal material obtained by amniocentesis. In order to develop a specific DNA probe, the regions coding for the gene of interest must first be isolated and characterized. Then, the nature of the genetic difference must be determined in the corresponding DNA from an individual exhibiting symptoms of the disease in question. A DNA probe may subsequently be constructed which binds specifically to altered DNA, but less well to the normal gene. Linking the DNA probe chemically to a radio-isotope tracer or other molecule that may be readily detected, such as biotin, can create a genetic test of high sensitivity. 37/

However, in cases where the difference may be a single base pair, the sensitivity of even a DNA probe assay may be insufficient. However, with the tremendous variety of restriction endonucleases available, even a single base pair change may create or eliminate a cleavage site for at least one of the known restriction enzymes. This restriction fragment length polymorphism (RFLP) may be detected by a relatively simple assay, which is especially promising when the sequences are known, and useful even when they are not. 38/

In some genetic diseases, the defective gene or its gene product, if any, is unknown. However, in some cases, another gene may be closely linked to the gene of interest. The linked gene may show up by a RFLP assay, as was recently shown for Huntington's disease, 39/ a rare degenerative disease of the nervous system that exhibits no symptoms until mid- or late adulthood. While it may be impractical to screen everyone for such rare diseases, the children of those with a family history of the disease may now be diagnosed long before the onset of symptoms. Such linkages may not occur in 100 per cent of all afflicted or carrier individuals, so it is preferable to find several such linkages if the gene itself cannot be identified.

The prevalence of a number of physical and psychiatric disorders has been correlated with the occurrence of certain other genetic markers. The human leukocyte antigens (HLA) are controlled by several genetic regions, with several allelic forms occurring at each site. More than 100 different HLA proteins have been identified. The prevalence of certain of these forms in association with disorders such as juvenile onset diabetes, rheumatoid arthritis, 40/ depression, 41/ and numerous others suggest that the presence of these markers predicts at least the susceptibility, if not the direct cause, to these disorders. It is not known if the HLA proteins themselves are involved in the susceptibility or are merely linked to the genetic culprit. However, it is

believed that many of these problems are of the auto-immune type, in which case the individual HLA proteins may indeed play a role. The application of RFLP techniques are being applied to define elements of the HLA region, thus allowing for the possibility of predicting details of an individual's future medical history.

(c) Agriculture

The application of recent developments in plant cell culture 42/ and gene transfer 12/ into plants to the problems of improved yield, pest resistance, reduced fertilizer requirements, accelerated hybrid formation, and stress (high salt, high and low temperature, low moisture) tolerance is receiving intensive study both in corporations devoted to agricultural products and in agricultural research institutes. 43/ However, the basic methodology has been available for a much shorter time than gene splicing techniques in bacteria and it is still being refined and improved. It is thus not surprising that there are still no applications ready for general use in this area.

(i) Agricultural microbiology

Microbiology, as it is applied to agricultural problems, has received considerable attention for a somewhat longer period, than attempts to manipulate the genes of plants themselves. A number of developments are relatively close to being available for the consumer. One area receiving widespread attention among the biotechnology firms in the United States is the improvement of strains of nitrogen fixing bacteria, particularly Rhizobium varieties which naturally form symbiotic relationships with legumes (beans, soybeans, alfalfa). 44/ In addition, a number of other soil organisms also fix nitrogen from the atmosphere, and with the co-operation of still other soil organisms, this nitrogen can eventually become available to plants. Strain improvement programmes are under way to develop inoculation that will increase soil fertility.

In addition to nitrogen fixation, there are other aspects of agricultural microbiology that are receiving attention. 45/ For example, strains of soil bacteria that produce substances toxic to certain soil pests, such as nematodes, or that produce plant hormone analogs that could stimulate the proliferation of plant roots, are also of great potential value to agriculture. It has long been known that the texture of soils and their chemistry are a direct function of the microbial action in soils. The fertility of soils, and their ability to sustain high yields of crop plants is not merely a function of the availability of mineral nutrients. In some instances, manipulation of the microbial ecology of the soil can have a profound influence on its apparent fertility. A broad approach to the engineering of soils and their resident flora could be of particular value to the agricultural economies of countries where the soils are of marginal fertility.

A variety of Pseudomonas, with the gene deleted that produces a protein essential for the nucleation of ice formation, was developed to protect certain crop plants from mild freezing conditions. 46/ The bacteria could thus protect plants from early frosts which can destroy crops shortly before the autumn harvest. Proposed field tests of this organism in the United States have been delayed because of a law suit challenging the environmental safety of this organism. 47/

(ii) Biological pesticides

One of the most attractive goals of biotechnology is the development of target-specific biological pesticides. The advantages of a substance that would destroy only selected species of insects or plants, instead of a broad spectrum of organisms, are many. Contamination of the environment and the food chain, the destruction of other species and the creation of ecological imbalances and toxic residues in food consumed, are all compelling reasons to develop an alternative technology to chemical pesticides. The bacterium Bacillus thuringiensis (BT) produces a toxin which, when consumed by many species of insects, is lethal. BT innocula have been used as biological insecticides for some years, although not nearly as extensively as chemicals. Some biotechnology companies are attempting to improve BT strains, and the cloning and expression of the toxin gene in other organisms is under investigation. 48/ BT is still, however, not particularly selective by itself.

The use of immunotoxins, with the antibody moiety specific for an antigen unique to a vital tissue of a single insect species is one model that has received some attention during the past two years. However, delivery of such a substance to the target tissue in the target organism poses great difficulties. One of the most promising substances in the design of novel insecticides is a class of viruses (bacillovirus) which attacks many insect species and which tend to be species or genus specific. 49/ The genetic manipulation of these viruses offers the prospect of direct biological warfare against insect pests. Another potentially effective biological approach to the control of insect pests involves the use of sex attractants called pheromones. Pheromone traps have achieved some success. However, the goal of the perfect species-specific insecticide is apparently some years away. Species-specific herbicides would seem even more elusive.

The inverse of the above strategy, namely that herbicide resistance could be added to a crop plant by appropriate genetic engineering, with the weeds then removed by the application of a broad spectrum herbicide, has also been suggested and at least one company (Calgene) has been working in this area. The possibility of adding the genes for naturally occurring plant toxins that are specific for certain insects directly to plants is also being explored, although it is recognised that such a toxin should be absolutely harmless to the consumer. 50/

(iii) Livestock improvement

Advances in mammalian in-vitro fertilization techniques as well as in the manipulation of the cells of the first few cleavages of a fertilized egg (zygote), offer new approaches to animal husbandry. The production of identical calf twins by separating zygote cells and transplanting them into surrogate mothers has been demonstrated. The gains made in the transfer of genes to mammalian cells, particularly to fertilized eggs, 11/ now make it possible to alter the genetics of mammals, although there is still much to be learned with regard to the precise insertion of new genes and the control of their expression. The use of natural and synthetic animal hormones to stimulate growth is being explored with interest in the production of cloned animal growth hormones as feed additives. 51/ The gene for rat growth hormone was successfully introduced into mice, resulting in animals twice their normal size. 52/ This technique may lead to a more direct method of producing larger livestock than generations of selective breeding.

(d) Industrial microbiology

The large scale fermentation of micro-organisms for the production of useful substances has become a central part of major industries in many countries, including the production of antibiotics, ethanol, enzymes, sugars, food products and flavouring agents. The expansion of industrial microbiology during the 1970s to include the screening and selection of many microbes suitable for the production of a variety of substances of value to the chemical, food or energy industries was given an additional boost by the advent of recombinant DNA methods and the refinement of plasmid genetics.

While most of the newsworthy developments in biotechnology during 1982-1983 were in the health and agriculture areas, research and development activities aimed at the improvement of industrial processes were expanded considerably during this period. Of interest are the construction of organisms which can produce the desired product directly (such as ethanol or glucose from biomass high in cellulose and hemicelluloses), or which produce enzymes that may be of commercial value themselves or can be used to catalyze specific industrially important reactions.

Activities in these areas are concentrated in the larger chemical, pharmaceutical and food products industries, many entering into research agreements with some of the independent biotechnology companies. Few of the small independents are engaging in self-funded research and development in industrial microbiology. In fact, some have curtailed or eliminated their programmes in speciality and commodity chemicals in favour of the apparently more lucrative human health products.

A few companies, however, have begun ventures in industrial enzymology, with the intention of developing innovative methods of modifying natural enzymes to make them better suited for particular purposes. For example, Genex has concluded a long-term agreement with Bendix to pursue general methods of protein engineering, and Genentech has formed a partnership with Corning Glass (Genencor) to produce improved enzymes. The Danish company Novo Industri, already specializing in enzyme production, is investigating methods for applying gene splicing techniques not only to the improvement of production processes, but to the modification of enzymes themselves.

(i) Biomass conversion

An area of industrial microbiology particularly appropriate to countries with abundant resources in trees or other cellulosic plants is the conversion of biomass (defined as plant material high in cellulose, hemicelluloses and lignin) into useful products. Much has been written about the potential uses of biomass, but little has actually been accomplished, particularly in the efficient and economical conversion of biomass to sugar, fuels or organic chemicals useful in other industrial applications. Some programmes for the industrial production of ethanol by the fermentation of starches and sugars have been under way for several years (the production of alcohol by microbial fermentation dates back to antiquity). However, these programmes are not true biomass conversion projects, and must use plant material that is also useful as food.

The key to biomass conversion processes are organisms that produce efficient cellulases, hemicellulases or ligninases. At present, most biomass derived primarily from wood must be pretreated to break down or convert the lignin or otherwise render the cellulose and hemicellulose available for

further reactions. The chemical and physical pretreatments in use today are expensive and require large amounts of energy. Thus, there are a number of research programmes today aimed at the improvement of strains that produce these enzymes. 53/ Some recent progress has been made in the search for effective ligninases. 54/

The favourite producer of cellulases is the fungus Trichoderma reesei. Strains of this organism have been found which produce many times the normal levels of cellulases. 55/ There are, however, many other natural sources of these enzymes which no one has investigated. This area, like many others requiring enzymes with very specific properties, may be a prime candidate for protein engineering. Once the enzymes are found, or can be created, it is then desirable to incorporate all of them in a single organism.

Biomass conversion technologies are at present not economically attractive to the commercial biotechnology organizations of the industrialized countries, but may some day be of great importance to developing countries. This is particularly relevant in the case of the production of fuels. 56/ At present, the most efficient of the biomass conversion processes to produce alcohol are barely competitive with the price of petroleum, which has been declining worldwide during the past year. However, improvements in the organisms, or, better still, the enzymes, that break down lignin, hemicellulose and cellulose, may some day make biomass conversion a principal source of hydrocarbon fuels in some parts of the world. 57/

(ii) Pollution control

One area of industrial microbiology that has received much recent attention is that of the control of industrial pollutants. Nature has provided enzymes which degrade or utilize virtually every natural organic substance and all but the most insoluble minerals. The novel man-made organic chemicals of the past forty years have, however, challenged the relatively rapid process of microbial evolution to adapt to hitherto unknown chemical environments. Thus, the environment has, in many areas of the world, become contaminated with "persistent" chemicals (meaning that they have no microbial predators). Many of these intractable substances are halogenated hydrocarbons, which include a large number of insecticides and herbicides, polychlorinated biphenyls (PCBs) and the notorious dioxin.

During the past two years, selection and screening methods coupled with plasmid engineering have yielded bacteria that do indeed attack some of these stubborn compounds, 58/ specifically the herbicide 2,4,5-T 59/ and PCBs. 60/ In neither case, however, has development of these strains been brought to the point where they are ready for use to clean up contaminated environmental areas. The first practical applications of such organisms are more likely to be at the source, prior to the release of industrial wastes into the environment, rather than to neutralize existing contamination.

One of the difficulties is that there is little economic incentive for investment in the development of practical microbiological methods of pollutant degradation. The pollution control laws in most parts of the world are such that the industries generating the offending chemicals can meet the required standards without seeking more effective methods. 61/ The burden of ill health imposed upon populations and the costs of disrupted habitats for wildlife from chemical pollution can be great to both individuals or government health programmes, and in lost income due to damaged resources, although this remains a dispersed cost. Until governments act to ensure strict pollution control standards, it is unlikely that there will be significant investment in the development of microbial pollution control.

Unlike the lack of incentive in economically advanced countries to develop vaccines for diseases prevalent in developing countries, the converse is true regarding hazardous chemicals and drugs. The strictest regulations for the protection of health and the environment are found in the most economically developed nations. The problems of environmental contamination and disruption in many of the developing nations are becoming very severe. It will be very costly to developing countries to neglect the control of pollution, even if it does not seem to be an immediate necessity. Biotechnology offers direct solutions to this undesirable by-product of industrial development; developing countries would be well advised to include this important area in their agendas when planning domestic biotechnology industrial development.

INDUSTRIALIZATION - 1982-1984

(a) From science to technology

Before the findings of the research laboratory become practical realities for the benefit of consumers, they must be translated into processes that are economically practical, are amenable to being scaled up to mass production dimensions and yield a product of reproducible quality. The difficulties in achieving practical scale-up were not fully appreciated by the scientist-founders of the first commercial organizations devoted exclusively to biotechnology.

The technical specialities required to achieve the development of efficient processes on an industrial scale have spawned what could be referred to in general terms as "bioengineering", providing for the biotechnology industry what the chemical engineer must do for the chemical industry. There are several areas of bioengineering in which significant advances have been made during the past two years, all helping to bring the concept of biotechnology as an industry into existence. These include (1) advances in the development of high yield expression vectors, especially for making mammalian gene products in bacteria; 62/ (2) the development of excretion vectors, 13/ both in E. coli and B. subtilis, that will greatly facilitate the large scale purification of cloned gene products; and (3) advances in cell and enzyme immobilization technology. 63/ There has been some progress in the modification of enzymes to make them more temperature stable, and therefore more suitable for large volume processes. However, the field of protein engineering - the design and synthesis of proteins for specific purposes - is in its infancy and will thus not have a significant effect on large-scale processes for another three to five years. 64/

However, the above methods, in order to be practical and economical on a large scale, require the precise control over the many parameters of the growth or reaction environments (temperature, pH, salt composition, energy sources, removal of waste products). Thus, there have been significant improvements in large-scale fermentors (for growing cells) and reactors (for biocatalytic processes), especially in the application of computers and robotics to achieve the precise control of processes for optimum yield and economy. 65/

(b) Industrial growth in developed countries

At the beginning of 1982, the private biotechnology industry, which had been undergoing rapid growth, seemed to be entering a period of somewhat slower growth, or even possibly was starting the expected "shakeout" - the period in which an overdeveloped new industry witnesses a reduction in the number of companies. This can happen by financial collapse, takeovers or mergers, resulting in a more realistic equilibrium, reflecting the size of an industry that can be sustained by the actual markets for the goods produced. This perception was created in part by the community of private investors, which had expected too much too soon from an industry that required many years of research and development before products would be sold. Even by 1984, the industry is far from being self-sustaining. There were cutbacks in some of the older companies (Bethesda Research Laboratories, Cetus) and some collapses (Armos, International Plant Research Institute). Companies going for public stock sales at the beginning of this period were also having to scale down their offers.

Nevertheless, the overall growth of the industry, measured in terms of total investment, has not really slowed after all. There is still a continuing substantial investment in biotechnology by venture capitalists and an increased commitment by the larger corporations who had been slow to seize the initial opportunities. The industry grew most rapidly in the United States at first. In the early 1980s, while American companies were enjoying record stock sales, European countries were trying to stimulate what seemed to be a sluggish biotechnology industry. However, after an initial infusion of government funds, the European biotechnology industry, at least in France, the United Kingdom, the Federal Republic of Germany and the Scandinavian countries, has grown rapidly during 1982 and 1983, as has that in Japan. At present, there are several hundred private firms throughout the world, both large and small, engaged in research and development in some aspect of biotechnology, depending on how the term is defined. A recent report of the U.S. Office of Technology Assessment 6/ identifies 219 specific companies in the United States alone and surmises that there are more that escaped being included in its census.

The extent of the establishment of a commercial biotechnology industry has reflected, more or less, the degree of economic development and the economic resources available for new investment in a country. The moderately developed but less wealthy countries (such as Spain, Yugoslavia and the Republic of Korea) are conducting research and training in modern biotechnology and genetic engineering, but are only slowly industrializing these methods. These countries are generally skilled in traditional fermentation technologies. The economically less developed countries have been accordingly slower in acquiring the skills of modern biotechnology or its industrial development. At present, there is virtually no biotechnology industry in the Third World exploiting recombinant DNA techniques or the methods of modern cell biology, although a number of these nations do have scientists in their universities and research institutions conducting high quality research in these areas.

(c) The transfer of biotechnology among nations

The discrepancy in the development of a biotechnology industry among the different nations of the world has been a matter of concern in recent years. This gap is exacerbated by the fact that many of the pressing needs of developing

nations are ideal subjects for modern biotechnology - vaccines against tropical diseases, protein-rich food sources, alternative energy and pollution control. 34,66/ However, the commercial industry is essentially market regulated, in spite of what some of the more idealistic entrepeneurs may proclaim. Only those areas are pursued which will presumably bring the greatest return to the investors. The problem, then, is how to bring the benefits of biotechnology to developing countries. Is it possible that a thriving biotechnology industry be developed in countries with little or no industrial development in other areas?

In fact there are many degrees of economic development, a roughly quantifiable term which tends to parallel standard of living indices such as literacy, personal income, infant mortality rate, and the fraction of the population achieving given educational levels. It is unlikely that a biotechnology industry would be developed in a country that has had little industrial development in other areas. Nevertheless, in spite of the overall economic statistics, many developing countries do have rather sophisticated industrial organizations as well as reasonably strong basic sciences in their universities to support an industry. It is these countries that are prime candidates for either multinational or United Nations promotional efforts or bilateral arrangements with developed countries.

With an advanced biotechnology industry becoming well established in the economically developed world, it cannot be expected that the lesser developed countries would attempt to start a biotechnology industry without making considerable use of the progress that has been made to date. In order for effective "technology transfer" to take place, however, there must be initiatives from both the developed countries themselves and from entities in the developed world willing and able to disseminate the necessary information and, perhaps, resources, to facilitate the establishment of domestic programmes in biotechnology.

As a first step in achieving the effective transfer of appropriate biotechnology to developing countries, a number of international conferences were held during the past two years, attempting to identify the problems of developing countries amenable to the approaches of modern biotechnology. A workshop sponsored by U.S. National Research Council, held in Washington D.C. in 1982, focused on tropical diseases, agriculture and animal husbandry, and energy. 34/ Two others held later that year in the Philippines focused on agricultural applications. However, for all of the agreement on what should be done, it has been much more difficult to establish the means or find the funds to begin the appropriate development programmes.

A number of industrialized countries conduct, as part of their foreign aid programmes, projects designed to further biotechnology in some of the developing nations. The United States State Deparment's Agency for International Development (AID) sponsors some bilateral programmes and sponsors the Board on Science and Technology for International Development (BOSTID) of the National Research Council. This independent arm of the U.S. National Academy of Sciences has sponsored numerous conferences and studies, and has just published a detailed study on the manufacture of alcohol fuels for developing countries. 57/

The World Health Organization (WHO) has been sponsoring research directed towards the solution of health problems in developing countries, such as the development of a vaccine for malaria. The United Nations Industrial Development Organization (UNIDO) has been active in several areas in promoting domestic biotechnologies in specific countries. Perhaps UNIDO's most effective current activity has been the sponsorship of national seminars and symposia in co-operation with specific countries. During these meetings, expert advisors meet with scientists, government officials and representatives of industry to help them in their planning efforts to establish a biotechnology industry.

The most ambitious international programme to date has been UNIDO's efforts to establish the International Centre for Genetic Engineering and Biotechnology (ICGEB). 67/ Since 1981, UNIDO has been attempting to establish a world centre of excellence in biotechnology research, development and training directed towards the needs of developing countries. It has been the aim of the architects of the ICGEB to attract the world's best scientists and technologists and, thus be in a strong position to carry out its intended purpose of fostering a biotechnology industry in developing countries. 8/ Up to the present, thirty countries signed the statutes establishing the ICGEB, most of them developing countries. At a meeting held in January 1984, it was decided by the Preparatory Committee to locate the Centre at two sites, in Trieste (Italy), and New Delhi (India). This decision was confirmed by a plenipotentiary meeting in April 1984.

The overall size of the International Centre, in terms of the number of scientists and bioengineers it will be able to support (a maximum of 30-40 at each site), is small in comparison with the world's major research laboratories or commercial organizations. Accordingly, it will be able to engage in relatively few programmes of its own. However, in order to achieve technology transfer to a much broader extent than would be possible through the Centre alone, independent research and development institutions in individual countries are encouraged to become affiliated with the ICGEB, thus becoming a part of its information dissemination network. The information programme of the International Centre is envisioned as one of its most important functions. One way in which the rapid, world-wide distribution of information is now being accomplished is through computer conferencing. 68/ An experimental computer network on the bioconversion of lignocellulose was established last year.

The efforts of UNIDO have greatly increased the awareness of many developing countries as to the benefits of biotechnology. China, for example, is establishing, with the advice of a number of scientists from abroad, three institutions for research, development and training in modern biotechnology.

It can be expected that the most effective way in which advanced biotechnology has already been developed in the industrial nations will be made available to developing countries will be a mix of several types of programmes, involving bilateral agreements with developed countries, foreign aid programmes, individual programmes of the United Nations and other international organizations (e.g., UNIDO, WHO, FAO, UNESCO, the World Bank), and large scale international programmes such as the ICGEB.

SAFETY REGULATIONS

The concerns among both the public and scientific community over the potential hazards of genetic engineering, at its peak around 1976-1977, 70/ have continually abated. That trend has continued into the 1980s, with the continuing relaxation of safety regulations world-wide.

While individual countries engaged in gene splicing activities have their own set of safety procedures and guidelines, most have been modelled to a large degree on the United States' National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules. 71/ The NIH Advisory Committee charged with continually examining the status of perceived risk due to recombinant DNA activities and the degree of protection appropriate to protect scientists, the public and the environment from any unreasonable risk of injury, has continually recommended easing the Guidelines and the removal of large classes of experiments from their coverage. Most countries have followed this pattern, both in revising the standards themselves and in reducing the complexity of the procedures to be followed by scientists. The strictest rules in force are those of Japan, although Japan, along with the other countries of the world, has continued to reduce the stringency of its standards.

Not all countries have regulations that are binding on the private biotechnology industry. The safety guidelines of both the United States and Japan apply legally to publicly funded research only. In both countries, the private industry has complied with the respective guidelines on a voluntary basis. The European Economic Community (EEC) adopted a set of non-binding guidelines in 1982, recognizing the need for uniformity among different countries. These are no more strict than the national guidelines of any EEC member nation. 72/

While the rules pertaining to the handling of organisms with regard to the prevention of human injury have eased over the years, a new type of concern has arisen during the past two years. Because many programmes, particularly in the agricultural area, are now ready to test genetically modified organisms in the open environment, the matter of ecological safety has become the most important regulatory topic. In the United States, the U.S. Environmental Protection Agency announced that it would regulate the release of gene-spliced organisms and their products through an authority designed for the control of toxic chemicals. No proposed regulations have been issued as of March 1984. When other countries are also at the stage of testing agricultural products, it is expected that these concerns will arise in such situations as well.

As there is no evidence of there being any unique hazard associated with the construction of genetic chimeras, it is expected that the safety rules and regulations will continue to be relaxed, perhaps eventually being abolished altogether; that is, unless there is a documented case of human injury or ecological disruption. In such an event, we may expect to see a reversal of the current trend towards continuing less stringency of the safety rules. 1/

OUTLOOK FOR THE FUTURE

The foregoing discussion has been a brief synopsis of the directions followed by world biotechnology over the two-year period 1982-1983. It has included a survey of the areas of technological concentration as well as the course of industrialization in both the economically developed countries and the developing nations. It is now appropriate to attempt extrapolating these current trends into the future.

(a) Technology

Because of the current rate of acquisition of fundamental knowledge concerning the structure and function of biological molecules and the cells and tissues they comprise, a number of new applications of this knowledge over the next few years may be expected that are sure to be hailed as "breakthroughs" in biotechnology. Some of the most important, which can presently be foreseen, are briefly discussed below:

(i) Molecular engineering

The speed and capacity of modern computers enable us to be able to carry out complex calculations that were impossible even with the computers of a decade ago. It is now possible, on the basis of mathematical models of the manner individual atoms and molecules form bonds, to compute the conformation and dynamical behaviour of entire protein molecules. 73/ At present, the theoretical approaches used are rather inaccurate approximations of reality. Only for rather small molecules is there close agreement between theory and experiment. 74/ However, there is intense interest in perfecting these methods, with the promise that in understanding these important properties of protein molecules, we will gain much insight into the catalytic activity of enzymes and the molecular basis for the biological activity of hormones, neurotransmitters, enzyme cofactors and immuno modulators. 64/

The capacity for making polynucleotides to order, and for the cloning and expression of any DNA sequence in efficient expression vectors, now enables us to synthesize proteins of any desired amino acid sequence. The knowledge of the relationship between function and structure will enable the design of modified or entirely new proteins with properties tailored to specific applications. In this way, proteins that do not occur in nature, but are useful to man's purposes, will be made in quantity. It is clear that the promise of the molecular engineering of proteins is so vast that it is destined to become a major activity of the biotechnology industry, probably in fewer years than many now predict.

Protein engineering can be carried out in smaller ways than by starting with theoretical predictions of the entire conformation of protein molecules. We already know a great deal about the structure and conformation of a number of economically important proteins. Focusing on specific portions of the molecule, such as the active site of an enzyme or the receptor binding portion of a hormone, can allow for limited manipulation of the molecule, based upon educated predictions of how desired functions will be altered if certain structural changes are made. 75/ When more conformational data becomes available, general properties, such as solubility, temperature stability and pK, may also be altered by the judicious manipulation of the composition of proteins. In the near future, protein engineering can be expected to be carried out by such limited approaches. Current research results are encouraging. As the theoretical understanding of molecular conformation and dynamics improves, so will the power of molecular engineering.

(ii) Human gene therapy

The perfection of methods of inserting new genes into mammalian cells has great potential for the correction of a number of human genetic disorders. Most accessible are those problems involving only a specific tissue type, such as the haemoglobin diseases (sickle cell anaemia, thalassaemia). 76/ The strategy involves the culture of the patient's own bone marrow cells, which then receive genetic surgery to correct the defect in the globin gene. These cells can then be cultured in quantity and transplanted back into the patient. While some premature attempts to do this failed, the procedure should work once methods for making the genetic repairs correctly are improved.

For other inherited disorders, involving developmental problems or metabolic defects in all of the cells of the body, a cure through genetic engineering may remain elusive. However, it may be possible to ensure that the carriers of such genes could have healthy children by using in-vitro fertilization methods and by correcting genetic problems in the fertilized egg.

(iii) Cancer prevention

While the pursuit of an effective cure for cancer, a disease that exists in a multitude of forms even within the same patient, may remain fruitless for some time to come, strategies to prevent cancer may be very successful in reducing the incidence of the disease. One line of research being pursued at this time is the development of accurate, sensitive diagnoses using monoclonal antibody methods. As in the case of attempting to design therapeutics using antibodies, the rationale for this approach depends upon the presence of unique cancer-specific antigens associated with cancerous cells. Preliminary results suggest that, at least with certain types of cancer, detection at much earlier stages than can now be done may be forthcoming in a relatively short time.

The ultimate goal in disease prevention, however, is to render an individual immune forever. If indeed there are unique cancer antigens, which occur only on tumor cells, the possibility of a cancer vaccine may be a fruitful approach. Of course, the body's natural defences against cancer are complex, involving specialized cells which recognize the "foreign" cells and destroy them. Recent research on the regulation of the immune system suggests that it may be possible to generally enhance an individual's immune competence, perhaps by methods involving the genetic modification of certain tissues, so that his resistance to cancer, and other diseases as well, will be generally increased.

(iv) Petroleum engineering

There are at present a number of scientists investigating micro-organisms that utilize the components of petroleum. A strain of Pseudomonas that would degrade the petroleum in oil spills 77/ provided the test case over which the US Supreme Court in 1979 determined that patents could be issued for living organisms. 78/ However, work since that time suggests that organisms can be developed to reduce the viscosity of crude oil in oil wells, which could enhance the recovery of much of the earth's petroleum reserves. 79/ Moreover, it is possible that microbes, or enzymes with the correct properties, could be found which would be useful in petroleum refining, thereby eliminating the need for expensive, energy consuming methods. Here is one case where molecular engineering may provide assistance to Mother Nature in developing the correct catalytic activities in a molecule that can function in non-aqueous environments.

A small number of ventures in this area are currently being established. However, it should be kept in mind that the practical problems facing those attempting to create workable technologies based on hydrocarbon microbiology are enormous. Thus, while this is likely to become an important area of biotechnology by the year 2000, it will take a significant commitment of time and research funding to achieve the goals set forth above. At present, it appears that only the major oil producers are willing to support major programmes in petroleum biotechnology.

(b) Industrial development

The commercial biotechnology industry continues to attract new investment and grow, even though the sale of products accounts for only a small fraction of its operating expenses. Because of the tremendous potential of the existing new methods and those still under development, the variety of applications would seem to be endless, with market economics determining the size of the industry. It is also likely that there will be significant encroachment of biotechnology into the domains of a number of other industries. Pharmaceuticals are obvious, but many less evident applications in the chemical and food industries are probable.

It is safe to predict that it will be some time before a stable equilibrium is reached. At present, there are far too many separate companies competing in the same areas for all of them to succeed in meeting their projections of market shares and future income. One may expect to see a levelling off of new ventures and some attrition of the number of present companies. Even through there seems to be plenty of risk capital available now, there will not be enough to follow all of the firms through the many years it may require before they realise enough sales to break even, especially for those concerns concentrating on products for human use. Mergers and acquisitions may be expected to be prevalent over the next five years, with the number of companies competing world-wide in any given area ultimately being far smaller than the present number. Successful management and foresight in planning will determine the survivors.

A biotechnology industry in developing countries can be expected to become established in those nations willing to make a strong commitment as an element of national policy. All such successful ventures will require close co-operation with governments or institutions of scientifically and technically advanced countries, as well as expert technical advisors. Those that try to build their own industry without help will simply not be able to catch up or compete. The gap has already become too great.

Those developing countries that wish to establish advanced biotechnology as a significant element in their economies have a much more difficult course to navigate than those in advanced industrialized countries. While international promotional programmes and bilateral agreements and foreign aid programmes may be useful and even necessary, there are not likely to be any quick solutions. The most important element will be for such countries to ensure that they have a significant number of highly trained scientists and provide them with the advanced (and expensive) tools of their trade. Education abroad, the present way in which scientists from developing countries receive their most valuable research training, should be increased, for the current

capacities of the universities in developing countries are not adequate to train enough people in the most current methods needed. Even if the proposed International Centre for Genetic Engineering and Biotechnology succeeds, its training activities will still be inadequate to train the requisite numbers of people to meet the needs of even those developing nations that have announced by the end of 1983 that they were planning a major effort to develop a domestic biotechnology industry.

Second to providing a strong science base and adequate manpower, the availability of funds is critical to the establishment of any new industry, and especially biotechnology. Contrary to some popular conceptions, biotechnology is capital intensive. At least that is true for industrial biotechnology embodying the most advanced methods of genetic engineering and cell biology, and the requisite facilities for production and product testing. Whether the funds come from government or private sources, they will have to be substantial if the industry to be developed expects to approach the standards that already exist in some parts of the world. This means that it will be very difficult for a country in the midst of an economic crisis to meet the demands of an embryonic industry such as biotechnology.

The implications of these requirements are that a sustained and substantial commitment to biotechnology must be made by any country hoping to succeed in establishing its own industry. This commitment must extend not only to the direct needs of the industry, but to education and training of its citizens, through specialized training abroad and the strengthening of its universities and schools at all levels. The planners must think not in terms of five years, but of at least fifty or one hundred years, and the view taken must be a broad one, encompassing many elements of the economy and society. For the success of biotechnology, or of any other new enterprise, is not independent of the future of the other features of any society. Those countries that can plan their futures most carefully, including those designated at present as members of the Third World, will be those achieving the success they seek.

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