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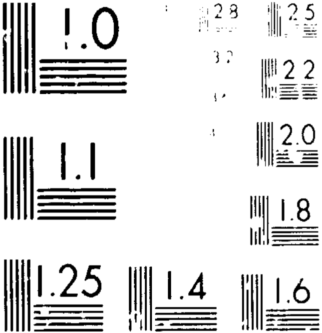
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THE POTENTIAL IMPACT OF MICROBIOLOGY ON DEVELOPING COUNTRIES*

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A. INTRODUCTION

In this study the horizon in microbiology is scanned for significant areas where the interactions between microbial genetics, enzyme engineering and fermentation technology are likely to forge biotechnology into a force for industrial adjustment and social change. The review tries to integrate the impressions gained from recent publications and from talks with academic colleagues with the conclusions drawn from the telling silence of scientists who are forced to protect classified information.

The state-of-the-art in microbiology and bioengineering, and its relevance to industry, particularly in developing countries, will be reviewed under five broad headings: fuel, fertilizer, food and fodder, health and industry. However, the study is introduced by three general chapters that hopefully will provide the reader with some understanding of the synergistic effects that will pave the way for future developments. The first of those chapters defines bioengineering in the context of its social relevance. The second explains some basic biological facts and their relation to salient scientific and technological advances in relevant fields (microbial genetics, enzyme engineering and fermentation technology). The third, finally, underlines the significance to developing countries of those areas and the consequent need for more effective information exchange and more extensive research co-operation aimed at industrialization.

It goes without saying that the forward-looking activities of some 70,000 microbiologists and an even larger number of biochemists, biophysicists, engineers, doctors and veterinarians, as well as those of the innumerable makers of bioconversion products such as wine, beer, bread and cheese, can only be discussed superficially and subjectively in a short report. Also, the author has been forced to trespass over many disciplinary borders in order to present some major trends in such a way as to stimulate discussion. These trends are projected into alternative scenarios which have been given a rather provocative profile. The scenarios are intended primarily to serve as reminders that breakthroughs in microbiology are subordinated to guiding forces generated by politics, and affected by decisions governing activities in schools, universities, farms and factories. As a consequence of an increasingly complex web of interactions and loyalties, these decision processes are not particularly well suited to the management of breakthroughs such as those precipitated in the fields mentioned above. In particular, their response tends to be sluggish when it comes to fostering the type of social innovation that may become necessary if we want to optimize the impact of the various inventions that now claim attention in the biological field. A review of the potential impact of microbiology may thus help to illuminate some basic weaknesses in international science and technology policy.

Ten years ago, entropy was a concept that was almost exclusively used by physicists, but now, when energy is a priority item among decision-makers, many economists and ecologists derive inspiration from the second law of thermodynamics. This law reminds us of the fact that all closed systems inevitably run down due to that unavoidable loss of order which we call entropy. The rate of decay can only be delayed by opening the closed system, and this is why the knowledge about how this can be done is occasionally now regarded as a powerful anti-entropic factor. But if the knowledge is limited to one system only, it is sterile, however detailed it might be. It is only when it interacts with knowledge contained in other systems that ideas are born. This is the essence of the entropy of ideas: creative thoughts disappear at the same rate as our understanding of the world around us is reduced. When that understanding is left to experts there may actually be little room left for the average person's creativity. Perhaps the new horizons opened by biomolecular engineering will help to make a new start towards an equitable and resilient society where we can visit our global neighbours without feeling either superiority and guilt, or inferiority and frustration. If microbiology can contribute to this goal, it will be a great achievement.

B. THE BACKGROUND FOR DECISION-MAKING

1. The focus on resource management and the quality of life

The attention given by the mass media to the turbulence caused by the current moves towards political independence often obscures the fact that a range of major problems, as well as powerful economic and technical forces, are leading towards increased levels of interdependence. Those two trends breed contradictions that inspire disputes which not only meet the disapproval of many young members of society, but also provide little time for considering the long-range impact of science and technology. This is quite a serious matter, since developments in areas such as microelectronics and bioengineering will obviously have dramatic and far-reaching consequences. Both rich and poor countries realize that such high-technology areas will sharpen the competitive edges between nations, but acute national problems tend to push their potential for solving major common problems into the background.

Both UNIDO's series of reviews of the implications of various recent breakthroughs and the new research programme of the EEC, F A S T (Forecasting and Assessment in the fields of Science and Technology), are now trying to compensate for this tendency to delay actions on problems such as those outlines in the GLOBAL 2000 report to the United States

President (1980). The programme will for instance consider European research strategies in the context of a future "Bio-society", a wording which reflects the high priority for biomolecular engineering which a number of governmental reports have recommended in recent years. This attention derives not only from the fact that the advances in the life sciences are now opening a new and exciting chapter of "Man's Place in Nature". These advances are also providing knowledge of strategic significance to resource management and quality of life. Renewable resources for satisfying basic human needs are emphasized, and the term quality of life highlights biological knowledge, not only in the context of health, but also as a catalyst for indigenous creativity and self-reliance.

2. Ethics and science policy.

The management of this knowledge provides an acid test for the maturity of the ethics governing science policy. The wave of concern which generated a research moratorium when DNA-hybrid techniques appeared is now subsiding, but a second wave expressing the opposite concern - how to accelerate the useful applications of genetic engineering - is building up. The wave front goes through a number of non-governmental organizations, which are now addressing the questions made urgent by the wide spectrum of conceivable applications. In a closing address at a recent bioengineering conference (Eastbourne, 6-10 April 1981). A. Humphrey put the problem in a nutshell by citing his grandfather: "The question is not whether there is a way ahead, but whether we have sufficient head for the way".

3. Bioengineering for development.

For developing countries, priorities are of singular importance in choosing activity profiles for bioengineering programmes. Bioengineering has its centre of gravity in applied microbiology, and more specifically in fermentation technology, but it is truly multidisciplinary and also has strong roots in biochemistry and chemical engineering. Bioengineering has been defined as the integrated use of biochemistry, microbiology and chemical engineering in order to achieve technical applications of the capacities of microbes and cultured tissue cells. Its industrial significance is emphasized in another definition stating that it is the industrial processing of materials by micro-organisms and other biological agents to provide desirable goods and services.

The microbiological laboratories needed for fermentation research, and for the genetic and enzyme engineering that provide the basis for modern bioengineering, are fairly simple compared with the facilities needed for nuclear physics or space research, but very expensive if compared with the facilities needed for traditional medical microbiology. Production processes are highly adaptable, an attractive feature which makes them more knowledge-intensive than capital-intensive. This suggests opportunities for developing countries, but it also highlights the significance of "bioinformatics", a subject that will be discussed in the following chapter.

4. Alternative scenarios for issues and priorities

Positive

- Governments agree on the need to use bioengineering as one of the means to reduce the debt burden placed on developing countries by increased fuel costs.

- At the United Nations Special General Assembly on Disarmament in 1982, governments agree on a major coordinated effort in microbiology, based on their committment to Article IX in the Biological Warfare treaty: "The States Parties to the Convention

Negative

- Microbiology is not highlighted as a strategic factor in development.

- The fragementation of microbiology in the academic world leads to wasteful competition and backlashes due to "overselling" of breakthroughs in various subdisciplines.

- Under-utilization of non-governmental organizations (NGOs) hinders the development of effecundertake to facilitate, and have the right to participate, in the fullest possible exchange of equipment, materials and scientific and technical information for the use of bacteriological (biological) agents and toxins for peaceful purposes."

- Under crisis pressure, it becomes obvious that all countries must participate in supporting the poorest nations and that the industrialized nations have a special obligation to apply R+D to the problems of developing ocuntries.

- Education in bioengineering is gradually improved by early schooling in the life sciences.

- Enlightened self-interest dominates R+D planning in bioengineering, and the problems related to physical and social limits to growth are gradually resolved.

tive networks for cooperation.

- Breakthrough areas are fostered primarily in the context of their significance to competition between countries.

- Inadequate attention on the part of governments leaves room for environmental and health problems to increase.

- The social costs of population pressures and of large-scale migrations increases rapidly and there is a gradual and contagious devaluation of human life.

- There are less and less inhibitions for using biological knowledge in warfare.

C. BIOINFORMATICS AS A STIMULUS FOR INNOVATIONS

1. The scope of bioinformatics.

The term bioinformatics has been suggested for the area of interaction between information technology and the life sciences, including biotechnology. As the means for defining the fundamental intrinsic characteristics of microorganisms and other cells in numerical terms became available, this area developed into an important service activity. It has provided structural and functional information on macromolecules and metabolites and developed the mathematical models that illustrate the dynamic interactions within and between cells. It thus helps the microbial ecologist to understand the digestion processes which occur both inside and outside the body, and it also indicates how complex phenomena in soil and water might be guided towards human benefit and resource conservation. Bioinformatics also tells the fermentation engineer where to find the best strains and substrates for a given purpose, and which "feedback" strategies are most likely to yield the desired industrial product. Finally, it provides the artificial intelligence which integrates the information from various instruments into identification labels for bacteria (numerical taxonomy), as well as diagnostic information for doctors and guidelines for biochemists and for the many industrial practitioners of applied microbiology.

2. Molecular genetics as a source of information.

Bioinformatics gained a new dimension when it was understood that all biological processes depend on genetic information stored as linear codes along gigantic chain molecules (DNA). The codes are universal and made up of four basic units paired in a characteristic fashion. Some 300 to 2000 such pairs make up a functional piece of information, a gene. The number of genes in a cell is determined by its functional requirements: a virus might need some 35,000 pairs of the basic building blocks, a bacterium 35 million and a human cell perhaps 35 billion. This makes for great differences in the length of the information strands, as well as in the "packaging" and reading of the messages. In higher, specialized cells, most of the instructions are normally kept silent except, of course, for the little segment needed for a defined function. In fact, in higher animals the silent regions have increased in size so much that nature has had to devise cutting and splicing procedures that transmit only selected instructions for translation into proteins, such as the molecules which accelerate the specific reactions that characterize the cell in question.

Such biocatalysts, or enzymes, function very much like the numerically controlled machining equipment in a group of factories that supply each other with tools, energy sources and prefabricated parts. In the same way as the machines perform millions of operations before they have to be replaced, each enzyme molecule can process large quantities of material before it has to be replaced. Provided with the proper raw materials (sugars, fats etc.) and energy sources (light or energy stored in chemical bonds) the cell shows a flexibility far beyond anything yet seen in industry. Industry cannot, for instance, rapidly reduce the number of machines to adjust the production capacity to market needs or to resource availability. A microbial cell can do this by making use of its storehouse of information molecules, and it also uses this information to copy itself rapidly until the environment has been exhausted or until competing organisms get the upper hand. The most successful information carried by one organism, or by a combination of organisms, is thus continually selected and multiplied.

Laboratory procedures devised to increase the genetic diversity in microbial populations and to improve the efficiency of selection for useful strains have long been used by applied microbiologists. They often involve the production of "mutants" through the destruction, by irradiation or chemicals, of the control mechanisms which the cell has developed over thousands of years to guard against wastage of energy or materials. A microorganism is thus produced which can serve well, provided that it is supplied with appropriate nutrients and is protected from competition with its more versatile relatives by means of a test tube or a fermentor.

The genetic engineers have now also made it possible to exploit the metabolic machinery of bacteria for producing molecules that are foreign to them. This fact has caused much concern, because such microorganisms can be regarded as "man-made" in the sense that, even if they had previously occurred in nature the new property would not have provided enough advantage for the corresponding information molecules to be maintained for very long.

3. Biological models for industrial practices

New knowledge about the behaviour of microorganisms and other cells under stress has influenced fermentation technology, as have also the results obtained by microbial ecologists studying the stability and versatility of microbial ecosystems. Defined mixed cultures for converting natural products into useful chemicals are on the horizon, and new ways to exploit microbial enzymes are continuously being reported.

Those facts underline the need for increased efforts in the metabolic mapping of known microorganisms and for goal-oriented selection and characterization of strains isolated from natural environments. The turnover of organic molecules is particularly high in the tropics, and this ecosystem may well represent one of humanity's largest untapped natural resources when it comes to biomass utilization and biofuel management.

Even though the advances in molecular biology have been impressive in recent years, much remains to be learnt about the production plans the cell follows when it assembles large protein molecules from a small number of building blocks: amino acids. Nature also provides thought-provoking models for planned obsolescence, for storing energy and for the recycling of old building blocks into new configurations.

The feedback principles, energy-saving practices and recycling methods used in modern industry show great similarities with the approaches that nature has developed by trial-and-error methods over millions of years. However, it is only recently that these approaches have started to make an impact in corporate boardrooms and elsewhere outside ministries for health and agriculture. It is for instance now realized that the biodegradability of products made by microorganisms offers a way to reduce the environmental stresses caused by synthetic chemicals. One begins to understand that nature's method of letting a sequence of reactions dovetail into each other over surfaces where the microenvironment or each step is neatly adjusted might eventually help the chemical industry to save a lot of expensive centrifuges, filters, and flocculation tanks. Nature's preference for continuous rather than batch processing, and its capacity to do without corrosive chemicals and high temperatures and pressures, further indicate how fuel, burners and heat exchangers might perhaps be saved, and how expensive tanks, pumps and valves might be replaced with simple equipment made from glass or plastic. Furthermore, the reduced vulnerability derived from operating on a smaller scale and with a wider spectrum of raw materials might well offset any sacrifices made in processing speed.

4. Enzymes as precision tools.

The enzymes which microbial cells use to break down large molecules were used early in industrial processes, but for synthesizing purposes the metabolic processes of whole cells had to be used first in regular fermentation processes and more recently in immobilized systems where the growth of the cells is restricted but their metabolism largely intact. However, better understanding of the ways in which cells precisely adjust the energy inputs into synthesizing processes is now opening the door to new approaches based on defined cell components. These might involve either membrane-bound enzymes or the special molecules (co-enzymes) that transfer electrons between cell locations where energy is either used or stored until needed. Some years ago it was found that electricity could charge some of the transfer molecules with high efficiency and also that certain important energy-rich compounds (ATP) could be made synthetically. Those facts, as well as the observation that some biosynthetic reactions are favoured when enzymes operate in abnormal solvent environments, indicate many new opportunities for industrial processes. The fact that substances insoluble in water can be attacked by microbial cells, even when the microbes cannot multiply, opens up a whole new field for biosynthesis. Cholesterol can for instance be oxidized by certain microbial cells even when they are suspended in carbon tetrachloride. The fact that cheap substrates, like sugar, can be used to regenerate the co-enzymes that drive the basic life processes makes it possible to modify expensive substrates by metabolic "hitch-hiking" on properly selected microbial cells.

The knowledge gained about the function of biocatalysts may eventually lead to the synthesis of molecules ("synzymes") with a higher stability than that which is desirable for a living cell. Recent advances in the immobilization of enzymes on electrode surfaces also make it reasonable to assume that ways will be found to open chemical bonds in such a fashion that electrons can be drawn off efficiently as an electric current. Such "biochemical fuel cells" might offer new approaches to the decentralized production of electricity from such easily available materials as alcohols, methane and ammonia. They would also offer novel approaches to the development of new types of environmental sensors.

5. The design and use of molecular probes.

Highly specific sensors using enzymes to detect and measure small organic molecules already have medical and industrial applications. They exemplify the type of instrumentation which is now continuously broadening the data base of bioinformatics.

Cumbersome physical techniques for the study of large molecules have been supplemented with immunological methods based on the use of pure antibodies (the body's highly specific defense molecules) made by fusing tumour cells that can grow very fast with other cells having the capacity to produce antibodies that bind to one trigger antigen only. Such "monoclonal antibodies" can be used not only to detect and measure very large molecules; they also open new industrial approaches to "drug targeting" and for immunotherapy. The latter can be considered in cases (e.g. cancer, rabies, some parasitic diseases) where the benefits might outweigh the small, but conceivable, risk that the preparation might carry a cancer virus. For the biochemist the greatest attraction of such antibodies is however that they can be used to "fish out" specific molecules from crude extracts of cells that manufacture desired products. Pure material can thus be obtained for analysis and for use as a model in the synthesis of the corresponding string of genetic information. This can be done by various techniques, some of which depend on the use of sophisticated laboratory robots.

The technique for determining the exact seq[illegible] of building blocks that makes up a gene has also developed very rapid[illegible] in recent years. Thanks to computer science and advanced instrumentation, it is now possible to "sequence" DNA at a rate of 200 pairs a day. Since this corresponds to a polypeptide made up of 67 amino acids it follows that the gene which codes for the average polypeptide (molecular weight around 35,000) can be mapped in a few weeks time. By backreading such information, the computer can also predict the structure of the messenger molecule that transmits the instruction from the gene to the protein building site in the cell. It can also predict the amino acid sequence of the polypeptide that will eventually emerge.

6. Benefits and hazards in bioinformatics.

Sequence libraries are gradually developing. They provide predictions about the positions where specific enzymes are likely to cut the DNA chain, indicate how molecular "bait" should look in order to "fish out" desired information strands from disrupted cells, and finally, guide the construction of genes that will be effective in a particular microorganism.

In view of the significance of such libraries, as well as of collections containing cultures of cells which produce monoclonal antibodies or vectors (a ring of DNA called a plasmid, or a virus) selected for their capacity to "package" and store large DNA fragments, more international coordination is needed. The knowledge and materials held in such libraries and collections represent the best chance to gain understanding about tumour development, metabolic diseases and autoimmune reactions, and they will also stimulate industrial microbiology. This is particularly true now that the initial concern about conceivable hazards has subsided, a consequence of containment methods and the availability of producer bacteria that are metabolically handicapped to the point where they cannot survive outside a protected environment.

Genetic engineering must however still be the subject of continued vigilance, not least in view of the fact that highly toxic compounds and their derivatives might well be produced as soon as their amino acid sequences can be used as a guide for DNA synthesis. If the result is an insect poison the social impact may be positive, but the result might also be an agent that shows a way to pass the borderline between biological and chemical weapons. Biological weapons are prohibited by an international treaty, but such treaties might well be disregarded by independent groups (guerilla movements, freedom fighters, terrorists and organized crime). In any case, the fact that modern wars often seem to be fought by proxy provides a disturbing perspective in a world that does not seem to be able to establish an international criminal law guarding against the misuse of science. The governments that watch over the Biological Weapons Treaty should of course monitor the consequences of genetic engineering, for instance the possibility to modify the identification characteristics of certain pathogens or to confine their spread to a defined target area by providing them with specific metabolic requirements.

Suitably modified synthetic or isolated genes can be attached to an appropriate vector, and a particle is thus formed which has the capacity not only to penetrate a microbial cell but also to force it to read the information provided and to translate it into large quantities of a desired product. The amount produced depends on the efficiency of the reading system and on the number of copies of genetic information available to the cell, now often increased by a technique referred to as gene amplification. The fermentation engineer can thus be provided with highly productive strains, with strains that make molecules characteristic of higher organisms and with hybrid strains that combine desirable properties from very different micro-organisms. The capacity to utilize cheap substrates will for instance certainly be combined with the capacity to produce hormones for plants, toxins for insects, and antibiotics for human beings and animals. As outlined in the following sections, genetic engineering also offers great opportunities for saving energy (e.g. biochemically or ecologically protected fermentations to circumvent sterilization) and for simplifying "downstream processing" (autoflocculation, transfer of a bacterial product to a filamentous organism, controlled leakage of desirable products etc.). In fact, the problem facing companies that specialize in genetic engineering is not to get contracts but to choose intelligently from among the projects offered.

7. The information needs.

Two keys are necessary to fully open the treasure chest of genetic diversity represented by the microbial kingdom that makes up one quarter of the total weight of all living matter (both plants and animals) in the world. One is the hardware of bioinformatics: information about how the analytical techniques, biosynthetic methods and genetic manipulations referred to above are performed. It also includes information about the availability of the microorganisms, vectors, chemicals and equipment needed. Examples are the computerized abstracting services and patent files, the World Data Bank on Microorganisms (Brisbane) and all the various lists of commercially available instruments, chemicals and enzymes that the microbial geneticist uses as tools to copy, cut and splice genetic information.

The other key is the software of bioinformatics: the quantitative metabolic information and analytical data that characterize various cells and organic molecules, and the mathematical models which illustrate their interactions. Examples are the computer programmes used to analyze the X-ray diffraction patterns which reveal the structure of large molecules; the mass spectrometer signals that sort out the composition of complex mixtures of chemicals; and the dynamics which explain ecological interactions and the behaviour of fermentations. A gigantic effort is needed to sift and supplement such information so that the full impact of biomolecular engineering on society can be realized.

8. Alternative scenarios for issues and priorities

Positive

- Centralized international facilities for computer-aided optimization of fermentations, for mechanized sequencing of amino acids and DNA, and for DNA synthesis hasten the appearance of useful applications.

- Sequence libraries and collections of vectors, insect pathogens and valuable clones of plants and antibody-producing cells stimulate activities in bioengineering.

- Coordinated studies are initiated in such areas as enzyme stability, co-factor regeneration and pretreatment of cellulose.

Negative

- The management of bioinformatics is regarded as a factor in commercial and national competition and the free exchange of information is curtailed.

- The character and quality of free academic research suffers from restrictions imposed by unbalanced emphasis on applications.

- Bioengineering activities in the industrialized countries emphasize high-key applications; low-key activities are regarded as unimportant.

- The dependence of the developing countries grows, both as a conse-

- Multiphase environments, directed mutations, thermophilic organisms and countermeasures against industrial hazards give dramatic results.

- The combination of mechanized metabolic mapping with computer analysis introduces new horizons in applied microbial ecology.

quence of imported values and techniques and because of the emigration of scientists who can not find adequate working conditions in their home countries.

- Culture collections are regarded as passive depositories and are consequently not given a stake in applied genetics.

- Screening operations and ecological bioengineering (i.e. the study of natural populations and the translation of the results into applications) are focused entirely on the problems of the rich countries.

D. THE IMPACT ON HUMAN SETTLEMENTS OF THE INTERFACE BETWEEN COMMUNICATION TECHNOLOGY AND BIO ENGINEERING.

1. Development through decentralization.

As indicated in the preceding chapter, the interactions between the life sciences and electronics are obviously generating a lot of information that will rapidly expand the horizons of applied microbiology. This should be scanned by the developing countries for information relevant to such problems as settlement planning.

As pointed out by Jean Jacques Servan-Schreiber in his book "Le Defi Mondial", which discusses microelectronics and communication technology, the fact that it has taken so long for an internationally oriented technology assessment to get started shows that our planning horizons are dangerously close. It also indicates that there is a grave risk that gaps between peoples and between nations are growing so rapidly that major conflicts will become inevitable. Since everyone would then be a loser, Servan-Schreiber advocates a major effort, a sort of Marshall Plan, that would help developing countries to use communication technology as a compass to find a short cut around the energy-intensive and environmentally stressful practices that paved the way for industrialization as we know it.

We all know that this process presupposes centralization and capital-intensive approaches which made the economy-of-scale factor very powerful. Certainly, the manufacture of electronic chips and various biocatalysts (microorganisms and enzymes) is also scale-factor dependent, but perhaps not to the same dramatic degree that we see for instance in the extractive and mechanical industries. The contribution of the products derived from such new technologies to the development of decentralized settlement patterns may well counteract any tendencies which the "biofactories" themeselves might have to encourage centralization and economic dependence.

Given appropriate political decisions, it is even conceivable that this counterbalancing effect on urbanization will prove to be their major contribution to development in areas such as Latin America, where more than 60% of the population live at present in the big cities. Slums and shantytowns breed crime, the diseases and the social unrest which paves the way for disruptive forces, but the social ills, such as unemployment, which seems to be an inevitable consequence of urbanization, are certainly not limited to poor countries. A quick look at drug addiction, infant mortality, venereal diseases and several other indicators for some cities of developed countries provides a forceful reminder of the fact that the gross national product per capita is a very poor measure of the "quality of life".

A reaction against urbanization has started in the US. Since 1970 the population in rural areas has actually increased 40% more than in the urban centres. People seem willing to work for less; they are better educated and their work performance is high. Consequently corporations are stimulated to establish highly sophisticated manufacturing plants in small communities. Electronics as well as communication and transport technology of course play important roles in this process, but bioindustries related to food, fiber and pharmaceuticals are also conspicuous.

The new trend found political expression at the end of 1980 when President Carter acknowledged that the back-to-nature movement was more than a fad. Alex Mercure, assistant secretary for rural development, also reminded his fellow countrymen that rural people use less energy, even when they travel long distances, "they burn wood for heat, they can better take advantage of solar energy and they don't commute as far as people in the suburbs". Similar views have been expressed by politicians in other industrialized countries, and the impressive group of scientists and engineers who presented their long-range view in "Europe 2000" seem to agree that decentralization is an important trend, and that do-it-yourself technologies ("machines replaced by tools") will attract more and more attention.

2. The birth of "equilibrium technology".

Against this background it is important to remember that biotechnology actually has two centres of gravity: one at the high-key end and the other at the low-key end of the scale of production processes. At the high-technology end we find large-scale brewing, antibiotics manufacture and various sophisticated systems for waste management (tower reactors, pressure-cycle reactors, compost factories etc.). These are normally quite scale-dependent and, unlike food fermentations and the practices in agricultural microbiology that illustrate the low-key end, they do not allow for much flexibility.

However, if the decentralization trend continues, a cross-fertilization between the high-key and low-key technologies is likely to spawn a new type of equilibrium technology as well as a new breed of "ecological bioengineers". Equilibrium technology is a projection of the drive towards self-reliance and self-governance which can now be noted at both the macro level (nations, regions and cities) and the micro level (villages and families). The mushrooming of "autonomous houses" (including greenhouses, solar and wind energy devices, heat storage units etc.) gives the bioengineer who is interested in process integration much food for thought ("about a starter-and-cartridge society"). Of course he realizes that such innovations still remain in the domain of the very rich and/or the very dedicated, but they may help to increase the general awareness about the shape of a future "Bio-society" and stimulate interest in the industrial exploitation of bioproductivity in the context of settlement planning.

An ecological engineer will look at our food as only one output from a vastly improved renewable resource base, and he will probably not take the current distinction between SCP (Single Cell Protein: just cell material) and MBP (Microbial Biomass Protein: cell mass plus residual substrate) very seriously. Rather, he would regard microbial protein. not as an end in itself, but as an important component of fodder mixes produced in such a way that they help us to achieve a high level of self-reliance, both with regard to food and fodder and to chemical feedstocks. The latter would be processed by a sequence of bio-conversions involving microorganisms or their enzymes, and when the catalytic potential of such agents had been exhausted they would constitute important protein sources.

3. Bioengineering and rural development.

The fact that a large portion of the world's population still lives in its two million villages explains the emphasis which many UN agencies are now placing on rural development as a means of reversing, or at least slowing down, the migration to the cities. The basic issues are obviously related to distribution rather than production, but this does not mean that scientists, engineers and inventors can sit back and refer the politicians to market forces and to existing knowledge about energy production, water management and agricultural practices. After all, the needs vary from one place to the other, so even though the problems may be global, the solutions must be local.

Experts on the three critical F's that will be discussed in the following chapters fuel, fertilizer and food must for instance think in terms of production patterns that differ markedly with local circumstances, even though those patterns also reflect what R. Critchfield has called " a universal village culture". This culture is a very fragile fabric which is easily torn if its adaptive capacity is overtaxed by inappropriate inventions or imported technologies. We must remember this when we consider all the opportunities and synergistic effects indicated by the recent developments in microbial genetics, enzyme engineering and fermentation technology. These areas should nevertheless be screened for inventions that might help to satisfy basic human needs, as well as for impulses for various social innovations that might help to combine such inventions into a coherent development pattern.

In the last century market forces demonstrated their efficiency as generators of inventions, but when those forces are as weak as they are in developing countries today, or when the impact of an invention is likely to take a long time to develop, we may have to devise other generators such as awards, government contracts and focused UN efforts.

The fact that many of these initiatives are now focused on rural development in poor countries makes good sense for two reasons. The first is that the special needs of settlements such as villages cannot generate market forces strong enough to compete - for the attention of inventors and investors - with the same forces radiating from urban centres. The second is that the industrialized countries are "hooked" on their investments (in infrastructure, education, established technologies, labour organizations etc). Consequently, even though they may be aware of their future needs and share the view expressed by such an eminent scientist as the late Nobel Laureate Dennis Gabor that "a satisfactory programmes for science and technology cannot aim at less than an equilibrium state in which only inexhaustible or self-renewing natural resources are used", they cannot let microelectronics, enzyme engineering and fermentation technology exert their full impact. Gabor also asks: "Who would subsidize research problems which will be urgent 30 to 100 years hence, when the principle of research grants is 'discounted cash flow'? At an interest rate of 7% a problem which will become vital in a hundred years is reduced to one thousandth compared with one of today". In the light of present-day inflation rates one certainly has cause to wonder if the industrialized countries will manage to develop the equilibrium technologies which they will one day need. Perhaps their only chance is to "learn by doing" i.e. by mounting a major research effort aimed at solving some of the staggering problems which the developing countries now face.

4. Towards integrated systems for biomass use.

When we talk about alternative sources of energy capable of replacing fossil fuels, biomass tops the list in many industrialized countries. Both fermentation of sugars to alcohol, and the production of biogas from waste have many advocates. They emphasize the reduced dependence on outside sources, and the positive effects which local energy sources can have on the employment situation. Economic considerations are important for such arguments, but they are normally based on current technology and tend to handle the potential of science and technology rather superficially, preferably as some percentage growth figure. Not only do such figures neglect breakthroughs in genetics and biochemistry, but they also tend to gloss over the significance of many factors, such as microbial ecology and process integration, which are critically important for the future of bioconversion technology.

To illustrate this point we might take the management of lignocellulosic material. This is the most abundant of all photosynthetic products, and the microbial ecologists used to regard it as so complex that a battery of microorganisms was needed to achieve a rapid and complete breakdown to useful chemicals. However they later found that defined mixtures of characteristic microorganisms can go a long way towards achieving the desired depolymerizations, and scientists at the National Research Council in Canada have recently even managed to convert cellulose to methane in a mixed culture of only three microorganisms growing in a defined medium. In fact, a fairly small number of microorganisms are required to achieve the initial decomposition of materials like wood and straw, and we now have a fairly good idea about the way in which certain of the active fungi operate.

One of the white rot fungi, for instance, offers the bioengineer the great advantage of being thermo-tolerant (optimal growth at 38-39°C). It can break down both cellulose and the tough "cement" in wood (lignin), and it can be made to produce a variety of mutants, including strains which have lost their capacity to break down cellulose. Such strains can be used to "loosen up" wood chips, so that energy can be saved when the cellulose fibers needed for papermaking are released by mechanical pulping. However, mutants might also be of considerable value for delignifying and upgrading straw and sugar cane bagasse to be used as cattle feed. The wild strains might however be preferred if protein were at a premium, since also the cellulose would then be attacked by the many enzymes available to the fungus. It might thus compete for attention with other microorganisms that are now used to convert the sugars in spent sulphite liquor into fodder protein. One reason is that this particular organism has proved well suited to utilize the effluent water from thermomechanical pulping as a substrate. The "white water" coming from a big newsprint mill might contain 25 to 40 tons of soluble substances per day (monomers, oligomers, lignins etc.). The Swedish Forest Products Research Institute has developed a continuous fermentation process which, at a residence time of about 17 hours, converts this nuisance into pellets that are easily separated from the culture solution by filtration. Based on waste water from a fiber-board factory, this process has now been scaled up on a 25 m^3 scale, yielding a fodder which has given positive feeding results particularly with ruminants. It goes without saying that much energy can be saved by the water recycling made p sible by such techniques.

5. Lignocellulose as a chemical feedstock.

The biodegradation of lignocellulosic materials operates best after physical or chemical pretreatment. This field is in a state of very rapid development, largely as a consequence of major world wide efforts to find inexpensive substrates for industrial alcohol production. Some of the techniques used are particularly attractive, since they widen the scope for such integrated processes as those just mentioned. Actually, they may be on the point of opening the door to the efficient use of lignocellulose as a chemical feedstock. One very attractive approach is the hydrothermal explosion of wood chips. This makes it possible to fractionate the wood into three fractions: the water-soluble material, which contains a variety of microbial substrates; the cellulose fibers, easily converted to glucose by enzymes; and finally, an alcohol-soluble fraction containing practically all the lignin. As a bonus, the latter is obtained in the form of a thermoplastic polymer which has great potential as a chemical feedstock. Microbiologists are also coming up with more effective enzyme producers, and the fact that they have managed to transfer into E coli the genes which code for the enzymes that attack cellulose indicates that genetic engineering is now entering the scene.

It is of course very unlikely that a single microorganism will ever be induced to become a hyperproducer of all the enzymes needed for the decomposition of complex lignocellulosic materials, but it should not be too long before mixtures of hyperproducers will provide nutritious protein from both lignin and glucose derived from wood and straw.

It is hard to guess which microorganisms will win the race for an economic bioconversion of lignocellulose, but it is probably wise to look for dark horses among the anaerobes which grow at temperatures as high as 60 to 72°C. In this group there are microorganisms that can make alcohol from cellulose and others that can make use of a very wide range of sugars as substrate. Recently, new isolation techniques have been developed which simplify the search for additional promising candidates among the microorganisms that decompose lignocellulose in nature.

It is also reasonable to predict that plant tissue culture for vegetative propagation will soon be used in breeding programmes intended not only to increase photosynthetic efficiencies (reduced photorespiration etc.) but also to facilitate bioconversions. Recent work on starch crops and on rubber, oil, and coconut trees is indeed thought-provoking. The cultivation of a very large number of small plants grown from cells derived from a carefully selected mother plant has in fact given a new dimension to horticulture and silviculture, where staggering gains in time over ordinary selection times are now being reported. As a bonus these new techniques also permit the production of virus-free cultivars of many species, including important starch producers such as cassava.

6. The need for new approaches in goal-oriented research coordination.

These few examples of front-line activities relevant to bioconversion might serve as reminders of the potential of bioengineering for turning the biomass resources of poor countries into powerful motors for rural development. However, our traditional academic approaches are hardly commensurate with the need for rapid progress in this field, and our methods for selecting priority areas also have many shortcomings. Fortunately the rapid expansion of the global telecommunication network now indicates that the time will soon be ripe for a new approach. There were three good reasons for the recent launching of a feasibility study* on computer conferencing, and for

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* A joint initiative by the UNEP/UNESCO/ICRO Microbiological Resource Center (MIRCEN) and the International Inventor Award (IIA), proposed to the European Federation for Biotechnology and in preparation through conferences organized by the World Academy of Art and Science (WAAS) and the International Development Research Center (IDRC).

using bioconversion as a model:

1. The rapid expansion of satellite communication with developing countries, coupled with reduced costs for electronic "packet-switching", as opposed to the increasingly expensive and unreliable postal services. Considering various means to foster technological co-operation between developing countries, UNDP some years ago asked the Inter-Press Service in Rome to study this matter. In the autumn of 1979 this organization, which uses a network of full duplex channels and telegraph subcircuits, submitted a report which showed 95 developing countries with either existing or projected satellite links. In view of the cost for INTELSAT segments and the recommendations made by various intergovernmental conferences, a tariff not exceeding USD 200 per month for a two-way, full-time dedicated circuit seemed to be a reasonable assumption at that time.

2. The need to improve international cooperation without dislocating the expertise in the developing countries more than is necessary. Computer conferencing of course provides a means to reduce travel costs without jeopardizing the efficiency of cooperation geared to specific missions.

3. The World Data Bank on Microorganisms and many other data banks holding information relevant to bioconversion problems can now be used as catalysts for cooperation. Various United Nations bodies of course noted early that their efforts to accelerate the development process in poor countries was hampered not only by weak infrastructures but also be communication difficulties influencing the progress of technology transfer. The UNISIST programme of UNESCO, for example, is aimed at interconnection of information systems and UNIDO has established an Industrial and Technological Information Bank. Some non-governmental organizations have also played a significant role in this field, in particular the International Development Research Centre (IDRC) in Ottawa, Canada, which paved the way for an effective interaction between developing countries by building a minicomputer-based network for exchange of inforamtion on development research (MINISIS). The initiation, by means of grants from this organization, of "Technonet Asia" has demonstrated the significance of mission-oriented networking to the developing countries.

7. The potential of computer conferencing.

In many countries the use of telephone lines for setting up voice communication between widely dispersed individuals at a predetermined time is common practice. Such contacts can be refined by the addition of telefacsimile for transmitting diagrams, and in some instances visual contacts can be established by means of video links. The extensive use of such facilities has so far been limited to the R&D personnel of transnational corporations and military establishments and to scientists active primarily in the geophysical and atmospheric sciences. However, the growth of data banks relevant to many other sciences has contributed significantly to the establishment of terminals at many large research institutes and university libraries. Thus a basic network already exists, requiring only a marginal addition of hardware and software for expansion into the field of computer conferencing. Even so, remaining problems related to standardization and administrative restrictions on communication should not be underestimated.

Computer conferencing represents the "star" approach to interaction by telecommunication. The computer is located in the centre where it serves as an information storage and switching device. Communication links radiate to terminals available to the "correspondents", who can be either conference participants or persons responsible for establishing local telephone contacts or workshops. Such contacts would be of particular importance in countries where the infrastructure is weak and where there are few of the committees, research councils, and academic and professional organizations that serve contact-generating functions in all industrialized societies. In societies where telex and telephone systems are extensive, the main attraction of computer conferencing lies in the fact that the experts involved can make their inputs and call for the comments of all other participants at a time, and with a frequency, of their own choosing and with minimal interference of language barriers. Participation also generates a sense of satisfaction, because views can be exchanged with other experts at closer intervals than those that can be achieved in the case of meetings between busy people. Normally such individuals also appreciate the lack of rambling and the matter-of-fact style which characterizes communication via a terminal. Also the risk for priority disputes in frontline areas is eliminated by the logged and printed records. Finally, computer conferencing serves an important auxiliary function, namely providing both direct and indirect access to data banks holding information relevant to the conference theme.

There is little doubt that the correspondents manning the terminals of a network such as that described above would function as important "bridge builders". Not only would they help to build bridges between the scientists and engineers in developing countries, and between those and the overcommitted experts in the industrialized world. They would also help to connect people facing similar problems, and they would broaden participation in the determination of the directions in which the efforts of genetic engineers and biotechnologists should be guided.

Participants in goal-oriented telecommunication groups would also play an important role in providing a gradual exposure to the overwhelming abundance of modern data banks. Gradual is a key work bere because creativity, which is the prerequisite for the development of appropriate technologies, is easily destroyed by information overload. However, it would certainly stimulate indigenous creativity if a microbiologist in a developing country could feed questions like the following into a network: What coating should be used for a digestor made from sisal cement? What cheap light-absorbing materials could be added to the beer fed to a solar alcohol still? Which mycotoxin tests, etc. could be made into simple kits for village use?

8. Alternative scenarios for issues and priorities

Positive	Negative
- Europe's limited surface, advanced infrastructure and traditions in research coordination makes the European Feder-	- Non-participation in decision-making increases distrust in experts and paves the way for excessive regulatory measures and

ation for Biotechnology take the lead in using computer conferencing as a tool for accelerating studies in bioconversion relevant to developing countries.

- The realization grows that bioengineering can have both an intermediate market, served by primary, large-scale industries, and a secondary, final market characterized by small-scale facilities.

- Energy analysis and ecological considerations stimulate the development of an equilibrium technology based on integrated recycling systems for utilizing wastes, low-grade heat and carbon dioxide.

- Friction between the materialism of the industrial societies and the post-industrial emphasis on a person's inner potential affects the content of education. Applied biology is increasingly regarded as a gateway to a meaningful use of "free time".

anti-intellectual attitudes, particularly with regard to genetic engineering.

- There are dramatic backlashes from accidents caused by gross neglect of industrial safety measures.

- Economic growth and consumption patterns increase dependencies at both the individual and national levels.

- Efficient cash crop management and mechanization increase energy costs and aggravate rural unemployent.

- The social costs of slums and shanty towns becomes excessive.

- Settlement pressures push biological systems beyond their carrying capacity and potential for self-repair.

E. FUEL

1. Wood as a fuel.

For a large proportion of the world's population wood is the most important fuel, but if present trends continue both the forest cover and the growing stocks of commercial-size wood in the developing countries will have declined 40% by the year 2000. By 2020 virtually all of the physically accessible forests in the developing countries will be gone. Wood products will become more costly, and the expected increase in oil prices will limit the penetration of kerosene as a substitute for fuelwood. In many parts of Africa wood is already so scarce that one member of each rural household must be diverted to wood-gathering, and in cities 20 to 30% of family income is spent on wood. Deforestation also depletes ground water, intensifies flooding and causes soil losses and silting of streams, reservoirs, hydro-electric dams and irrigation works. Combined, these factors adversely affect biological productivity and, in the long run, will also reduce the diversity and vigour of the gene pool represented by the plant and animal species that are now losing their habitats, especially the tropical forests. Hundreds of thousands of species, perhaps as many as 20% of all species on earth, are at peril if the present trends continue. Add to this the possible disruptive effects on agriculture and forestry of increased levels of atmospheric carbon and sulphur oxides caused by the burning of fossil fuels, and it becomes evident that effective biofuel management must be a central global concern. After all, this fuel can be produced almost everywhere, recycles carbondioxide, is low in sulphur and traps solar energy in a form that can be stored, transported and easily released as heat.

In the industrialized countries the elimination of telephone directories, introduction of electronic newspapers and extensive use of magnetic memories as well as widespread recycling of paper and substitutions in the building sector will certainly help to save wood, but this will probably be balanced by its increased use as a chemical feedstock.

2. Biofuel perspectives.

Biotechnology will influence the use of biomass as a fuel in three ways: by increasing the amount of biomass available, by improving its conversion into versatile fuels and by reducing the pressure on existing energy sources (energy-saving processes and improved recovery of fossil fuels).

The amount of biomass that can be used as fuel depends on the level of bioproductivity and on the efficiency of recycling. Both these factors can be influenced by bioengineering, as illustrated by the following incomplete list:

- Plant tissue culture and screening of efficient solar energy converters among algae and photosynthetic bacteria.

- Integrated systems for optimal use of energy forests and aquatic environments.

- Production of pre-fertilized and pre-protected plantlets and of photosynthetic starter cultures.

- Containment systems for efficient use of water and carbon dioxide for plant growth.

- Microbial inoculants for improving the use of soil nutrients such as phosphorus, and for stimulating biological nitrogen fixation.

- Biological control agents for protecting energy plantations.

- Management of biomass in such a way that the energy content of any material remaining after the extraction of food, fodder, fiber and oils, and/or after digestion by the animal, can be effectively utilized.

The last approach is particularly important since it can help to balance the trend to use food (maize, roots and tubers) as a substrate for the production of gasoline extenders or substitutes. Food security for the poor should not be replaced by liquid fuel security for the high-income groups in a country.

There are several techniques which permit the conversion of all biomass into either gas or various types of liquid or solid fuels (e.g. charcoal). However, since such techniques require both a feed-stock of relatively low water content and high and uniform temper-atures, they tend to be capital-intensive -- even though fairly simple mobile gasification systems early demonstrated their useful-ness for running combustion engines. In fact, some people claim that they might still compete with biological systems at the village level, and might thus be an appropriate product for manufacturing in devel-oping countries.

Fermentation products such as methane and alcohols, however, offer an alternative for converting a wide range of materials into versatile fuels. In addition to regular energy-rich starch crops, waste from sugar factories, distilleries, vegetable-oil refineries and food industries can be considered, as well as municipal garbage. A number of efficient solar energy converters that demand only marginal resources are also attracting attention. Water hyacinth, a nuisance plant with an impressive productivity (850 kg/ha/day dry weight has been reported) is one example; but giant kelp, elephant grass and algae grown on sewage may also become useful energy sources. Because such biomass often has a fairly high water content, bioconversion is more attractive than physical conversion; it also helps to reduce disposal costs. Digestion aimed at biogas production is particularly important since it can be applied on both small and large scale, and also because it can be used for a variety of materials that would otherwise constitute a hazard (fecal matter) as well as a resource waste (energy and nitrogen loss).

3. Biogas.

The production of biogas (methane diluted with carbon dioxide) has the advantage of eliminating a separation problem which cannot be avoided in the preparation of liquid fuels. However, mobile use is limited when the gas is produced on such a small scale that compression into cylinders becomes too costly. It is then used mainly for cooking and lighting, even though farm application might occasionally include running tractors and water pumps from easily transportable gas bags. Bags have also been used as digestors, but much research remains to be done before optimal reactor designs and materials can be selected. Current studies on multi-stage, plug-flow, fluidized and expanded beds, fixed film reactors etc. show that simple but efficient systems can be designed for greater stability, higher throughputs and better conversion efficiencies than those now common in small-scale digestors. This offers a challenge to both the engineers - who must develop simple methods for maintaining the right temperature and proper hydraulic conditions - and to the microbiologists. The latter must always remember that effective biogas production requires the sequential action of microorganisms that must be present in the right proportions even if they have different growth characteristics.

If the conditions are right, up to 70% of the combustible energy in organic matter can be converted to methane. (With cattle waste some 4,5 litres of gas are produced per litre of reactor material per day.) But when the substrates are diluted they require large digestors, and when the proportion of solids is high the energy requirements for mixing and pumping go up, scum formation may be a problem, and the optimal concentrations of the ammonia and organic acids that are produced in the process become difficult to maintain. However, new types of unstirred fixed film reactors, recently developed for swine manure at the National Research Council in Canada, indicate how simple and efficient reactors might be designed in order to cope with large variations in load and temperature. For very large scale conversion of city garbage, new techniques for extracting gas from landfills are also available. Large-scale anaerobic treatment of city sewage, before the organic matter is oxidized and partly recirculated, also holds great promise as an effective means to retain nitrate and phosphorus.

4. The potential of integrated energy production systems.

Twenty to 70% of the material passing through a digestor is destroyed, and the percentage can be increased by mechanical disruption before fermentation or by pretreatment with acid, alkali or enzymes. A proper balance of substrate inputs and the use of appropriate starter cultures (either flocculating or tending to adhere to surfaces) can also improve performance. In the long run, genetic engineering may also help in the establishment of stable mixed cultures adapted to particular wastes or to green plants selected for their efficiency as solar energy bioconverters. These might for instance be marine plants fed by sewage or by nutrient-rich bottom waters. The latter approach is particularly attractive, since it permits a simultaneous exploitation of the thermal gradient in the ocean. This might run a turbine generating electricity for pumping, a vacuum still for producing fresh water and an aquaculture system for producing high-value protein such as shrimp.

Other types of integrated energy production systems have also been suggested. One visualizes the burning of algae produced from sewage in shallow lagoons on top of gigantic floating polythene sheets. The combustion would proceed in a magnetohydrodynamic system that would fix nitrogen, and the ashes would be returned to the lagoons as nutrients. Another concept is to use algal ponds for hydrogen production. In this case the cells would be transferred to a reactor where their enzyme systems could split water before the exhausted cells were either rejuvenated or digested.

Other systems for biophotolysis are more sophisticated and will take longer to develop. However, it should be noted that the photosynthetic apparatus from plants functions for some time after immobilization in films, where the light energy normally used by the plant for building up carbohydrates from carbon dioxide energizes a microbial enzyme capable of splitting water. This process, of course, yields oxygen as well as hydrogen, and since many of the components in the system are very sensitive to oxidation much thought is now going to the stabilization of the active molecules and to the design of configurations with separate compartments for oxygen and hydrogen release. Progress is rapid in this field, as are the advances in the development of equipment for storing light energy in algal biomass. Efficiencies go far beyond anything yet seen in agriculture. Whereas an efficient energy farm based on rapidly-growing trees might not produce much more than 15 tons/acre/year (about 9 million litres of alcohol) algae production might well reach 60 tons/acre/year (about 70 million litres of alcohol), and certain varieties can also produce hydrocarbons in high concentrations.

5. Transport fuels from biomass.

Like aquatic energy plantations, terrestrial energy farms belong to the future (in some countries the near future) provided, we are talking about willow, poplar or other rapidly-growing trees. Sugar cane and some crops like maize and cassava, however, are already providing substrates that are converted into industrial alcohol. In Brazil the production level is now four billion litres per year, and is expected to reach 11 billion by 1985. Cane juice is the primary substrate, but molasses and cassava are also used. Together with potato, yams and taro, cassava is an important source of starch in the tropics. Fruits such as banana, citrus, apples and grapes can also serve as fermentation substrates for a spectrum of products ranging from low-priced industrial alcohol to expensive beverages. The former is now primarily used as a pure fuel for combustion engines, as a gasoline extender, or as a replacement for traditional additives used for octane value improvement. In principle, however, it can also serve as feedstock for the production of small molecules such as ethylene and acetic acid, or for making polymers such as polyethylene and PVC.

Butanol is another fermentation product which is now receiving attention as one of many possible diesel oil extenders. Many vegetable oils can also be used in diesel engines, and this underlines the importance of various microbial enzymes that might improve the efficiency with which such oils can be extracted and of integrated energy production systems where the waste products can be used.

6. Advances in the production of industrial alcohol.

When the starting point for making industrial alcohol is starch, wet milling is normally the first step since this permits the separation of valuable byproducts (gluten and corn oil). This is followed by heating to disrupt the starch grains and by acid and/or enzyme treatment to produce glucose. The advances in this area have now reached a point where starch is rapidly becoming competitive with cane sugar even if this carries with it an extra energy source (bagasse) that can be used for the distillation process.

The sugar is normally fermented with yeast, but it has been demonstrated that higher productivities can be reached with certain bacteria capable of receiving DNA vectors from other bacteria (a memento in the context of genetic engineering). Since 1978 much research has gone into the design of bacterial plasmids that carry a yeast chromosomal gene marker and which can also be amplified in E.coli before being inserted into yeast cells. This work has largely been focused on the transfer of genes from higher animals in such a way that they attain high stability, but it can be assumed that strains which directly ferment starch, cellulose and lactose will eventually be produced. Yeast cells engineered to convert 5- and 6-carbon sugars with the same ease would be particularly useful.

The fact that some bacteria that grow well at very high temperatures carry plasmids that are stable in the course of continuous cultivation also indicates a possibility of developing industrial fermentations for the production of alcohols at high temperatures. This is very important for the economic separation of the alcohol from the beer, as is also the use of cells that tolerate high concentrations of sugar (>25%) and alcohol (>12%) or of the solvents that might be used instead of distillation for removing the product.

To these obvious goals for the genetic engineer are added certain desirable characteristics that are compatible with cheap and efficient reactor designs, like beds containing cells that perform well when immobilized at very high densities in or on various carriers (e.g. chips of sugar cane or gel beads derived from polymers extracted from certain seaweeds). Such systems normally take the form of columns where the substrate (for instance grape juice or barley malt wort) goes in as a continuous stream at one end and the product (such as an alcoholic beverage) comes out at the other. The throughput is adjusted so that all the sugar is used up, which might take a few hours. Such columns might be stable over months if the yeast cells are rejuvenated every few weeks with a nutrient solution.

Similar systems can also handle liquid wastes, such as whey from cheesemaking or spent sulphite liquor from paper factories. Solid agricultural or paper wastes must first be solubilized, but, as mentioned earlier, there are great hopes that this might eventually be achieved cheaply and efficiently with microbial enzymes. This would open the road to simple systems suitable for producing liquid fuels going to "captive markets" like local bus systems or farm equipment. The fact that even industrial alcohol produced from easily converted materia' ich as sugar or starch still requires governmental subsidie. ax benefits in order to be competitive with conventional liquid fuels, however, demonstrates that big efforts are required before the fermentation route can be chosen for making freely competitive liquid fuels from lignocellulose.

7. Geomicrobiology as a means to save energy

The many potentials which bioengineering offers to save transport and process energy by introducing novel production techniques and fermentation equipment are discussed in other chapters of this study. However, the potential of microbiology for saving energy otherwise needed for concentration purposes, and for stretching available fossil fuel resources, should be underlined since genetic engineering can be expected to influence both areas. It is for instance known that improved bacteria for the leaching of minerals such as copper and uranium can be produced. Certain microorganisms are also very effective in concentrating phosphorus, and others enrich valuable trace elements that can then be recovered from the ashes when the cells are incinerated. Even the low concentration of uranium in seawater might eventually be economically recovered. Still other microorganisms produce polymers with a remarkable capacity for binding heavy metals, an important fact in view of the environmental loads caused by such metals when they are released by increased human activities, especially intensified fossil fuel use. However, one can derive some consolation from the fact that microorganisms might perhaps also help to remove one disturbing element from fossil fuels even before they are burnt, namely sulphur.

8. The stretching of available fossil fuel resources.

Finally, it should be noted that bioengineering can be expected to play an increasingly important role in the extraction of the planet's remaining stock of fossil fuels. Most "empty" oil wells, for instance, still contain large quantities of oil trapped in porous rock. Since this rock is normally calcareous, microbial acid production may be used to release carbon dioxide gas which will force the oil droplets out of the rock. There are also certain microbial products which make the oil flow easily, and genetic engineers have no doubt already started to design bacteria with the desired combination of properties. One particular bacterial polysaccharide has long been considered for tertiary oil recovery, but the high temperature found in many oil wells is a challenge, as is also the fact that the microorganism in question happens to be a plant pathogen. However, the gains possible in this field are so enormous that great efforts to circumvent the obstacles are likely This is also true with regard to the search for microorganisms capable of decomposing crude oil at low temperatures, and for cheap nitrogen and phosphorus compounds that would enrich the substrate at the oil/water interface.

The production and use of microorganisms that utilize carbon compounds from plant roots in exchange for minerals and water mobilized from the soil might also become important for the restitution of land damaged by strip mining for coal. Such environmental activities may become increasingly important as means of overcoming public reaction against some aspects of fossil fuel use.

9. Alternative scenarios for issues and priorities

Positive	Negative
- Coordinated research efforts to improve biogas technology and make lignocellulosic materials attractive as raw materials for liquid fuels.	- Existing biogas technology is regarded as definitive, or at least good enough for agricultural use. Reported as insignificant in national energy budgets.
- The experience gained from various types of energy plantations gradually makes them attractive also as sources of chemical feedstocks.	- Energy plantations are opposed because of their limited significance in total energy budgets. Their importance as a stepping stone towards biomass as feedstock is neglected.
- Increased vegetable costs and improvements in greenhouse technology and CEA (Controlled Environment Agriculture) make recycling of carbon dioxide and use of waste heat from fermentation plants and cement factories attractive.	- Opportunities for energy saving through integration are neglected, since they clash with traditional settlement planning. - Decentralization trends are opposed as fads or fantasies.
- The need for integrating energy production with mineral recycling and nitrogen fixation is acknowledged.	- The "global grain basket" gradually shrinks as crops are diverted to industrial alcohol production.
- The initiation of industrial activities requires supplementation of environmental	-Growing concern about release of CO_2 and SO_4 causes badly prepared and very costly crash programmes.

impact statements with social impact statements.

- Oil spill management and tertiary oil recovery are greatly improved by microbiological means.

- Microbial photosynthesis in protected ocean waters is gradually increased as terrestrial energy plantations are forced into marginal areas where planting, harvesting, irrigation and fertilization become more difficult.

F. FERTILIZER

1. Microorganisms and soil fertility.

The significance of digestion processes for methane production was mentioned in the preceding chapter. Their potential for turning out fertilizer may be even more important in areas lacking the substantial amounts of fossil fuel and capital required for conventional fertilizer manufacture. This becomes obvious if we consider the situation of an Indian farmer producing 30 m^3 of biogas per day from 50 kg of human and animal fecal matter. The effluent from the simple equipment needed for this operation can be used for irrigation or fish cultivation, and the sludge produced has a fertilizer potential corresponding to an annual use of some 100 kg of urea, 250 kg of superphosphate and 50 kg of potassium phosphate. Since the sludge is an organic material, it improves the soil structure and releases nutrients fairly slowly. It also helps to maintain soil humidity and reduce runoff, and thus counteracts two serious consequences of exploitative agriculture. This tends to neglect the use of slow-release inorganic fertilizers because of their costs, and also impoverishes the soil ecology by an excessive application of agrochemicals. These are two of many causes of the desertification which is now progressing at a rate of 6 million hectares a year (a rate which will have expanded the world's deserts by 20% over the next twenty years).

As indicated in the preceding chapter, bioengineering might eventually develop advanced biological systems for trapping solar energy in desert areas, but there are a number of more immediate possibilities to counteract desertification. Some are related to microorganisms that help to support pioneering plant species, others are related to plant tissue culture used as a shortcut in the development of species tolerant to acid or alkaline soils, high salt concentrations or long periods of drought. Such plants might well be supported by microorganisms that can fix nitrogen from the air, extend the root system of the plant or counteract pathogens. Genetic engineering could play an important role in such developments, but there are also a number of methods that are immediately applicable. They include the production and distribution of effective inoculants for the seeds of plants that have developed special systems for protecting and feeding the appropriate "symbiotic" nitrogen fixers and for utilizing the nitrogen which those plants extract from the air (soy, peanuts, alfalfa, clover etc.). Such systems are not limited to commonly exploited plant species, but are also found in others, some of which cooperate with microorganisms that have only recently been cultivated. There is obviously much scope for innovative inputs from plant and microbial geneticists and for those industrial microbiologists who face the challenge of large-scale production of stable inocula. Free-living nitrogen fixers such as certain algae are already being used as fertilizers.

2. Biological nitrogen fixation.

In the longer perspective it is conceivable that the genes which code for the enzymes that control nitrogen uptake and attachment to the plant roots will be exploited for important grain species. Vectors like plant viruses, or a certain bacterial plasmid that causes tumours in plants, might then be used, but a number of difficult problems remain to be solved and one will never be able to circumvent the fact that the fixation process will rob the plant of a substantial amount of its photosynthetic products. It is now known that a bacterium needs more than a dozen genes to fix nitrogen from the air, but much remains to be learnt about the plant genes that play a part in the acceptance and protection of the active bacteria.

3. Alternative scenarios for issues and priorities

Positive

- Regional energy analysis greatly influences the planning of fertilizer production.

- Stabilized Mycorrhiza inoculants are produced and widely distributed as supplements to nitrogen fixer/plant pairs of certified efficacy.

- Coordinated development of more efficient and simpler biogas reactors is supported by tax benefits based on fertilizer output.

- Short-loop recycling reduces fertilizer needs.

- New nitrogen-fixing grains are introduced.

Negative

- Energy dependencies increase due to expansion of inorganic nitrogen production.

- Soil and phosphorus losses and environmental impacts of the nitrogen oxides and heavy metals associated with fertilizer use add to the polarization between "big business" and environmentalists.

G. FOOD AND FODDER

1. The urgent need for action.

The arable land surface will have increased only 4% by the year 2000, but food production is projected to increase 90% over the years from 1970 to the end of the century. This means that most of the increase is expected to come from more intensive inputs of technologies such as fertilizer, pesticides and irrigation. The real prices for food are expected consequently to double, and since the bulk of the increased production is likely to go to countries that already have a fairly high per capita food consumption, the situation will scarcely improve in South Asia or in large areas of low-income North Africa and the Middle East. Per capita consumption in the sub-Saharan African countries is actually likely to decrease. This means that vulnerability to irregularities in the climate, to market fluctuations and to interferences with the distribution of food aid will increase. The volume of food aid may also be adversely affected by such factors as large-scale diversion of grain to motor alcohol production and by a growing concern about soil losses and environmental repercussions in the producing countries. Considering not only the loss of lives caused by famines, but also the fact that insufficient food may prevent children from reaching normal body weight and intelligence, it is obvious that major coordinated efforts are called for.

In the preceding chapters some examples of microbiology applied to bioproductivity were cited, for instance the possibility of increasing the fodder value of agricultural waste materials or of supplying plant nutrients in the soil. However, there are many other areas of food and fodder production where applied microbiology and bioengineering can be expected to play a significant role: biological insect control, veterinary medicine, post-harvest and food technology and finally, single-cell protein (SCP) production.

2. The control of insect pests.

An increased use of pesticides seems to be a prerequisite for rapidly increased crop yields, particularly in developing countries, where pesticide use is expected to at least quadruple over the 1975 - 2000 period. Persistent pesticides already adversely affect fishponds in some parts of Asia, and 15 out of the 25 major pests that are found on Californian farms are now resistant to one or more types of pesticide. This fact, together with severe reduction of the natural enemies to the pests and of important pollinating insects, makes it likely that increased attention will be given to the use of microbial agents that attack a narrow range of target species. Such agents also have a great potential in the fight against many of the disease vectors that limit the areas suitable for meat production (tsetse flies) or interfere with a person's working capacity (malaria mosquitos). There is certainly no lack of pathogens to choose from: 100 species of bacteria, 700 viruses, 300 protozoa and a large number of nematodes; but only a few have so far attracted the attention of the bioengineers. Actually large scale production of many insect pathogens is quite difficult, and the safety testing must of course be extensive.

There is nevertheless little doubt that co-ordinated efforts of bioengineers, applied microbiologists and genetic engineers could open many new roads towards improved insect control. They might even incorporate the use of persistent chemical agents, provided that effective microbial agents were available for decontamination. Recent studies indicate that specialized strains might even be developed to deactivate 2-, 4-, 5-T and such dreaded chemicals as dioxin. A bacterium which causes tumours in plants also has great potential for introducing genes controlling not only resistance to insect and microbial pests but also to herbicides.

3. Microbiology and the production of animal protein.

Genetic engineering will undoubtedly provide veterinary medicine with many new hormones, vaccines and antibiotics that could have quite a dramatic effect on the production of milk, meat and fish. One example is the recently produced bovine growth hormone that may hopefully increase milk production by as much as 10 to 20%. Another is a new coli strain which has been transformed into an effective agent against diarrhoea in calves and pigs. Some of the foot-and-mouth virus antigens have also been produced in coli, but their usefulness is somewhat more dubious in view of the potency of the vaccines that can be produced with relative ease in many-thousand-litre batches of suspended tissue cells.

The possibility to manipulate the microorganisms in the digestive tract of herbivores indicates challenging opportunities to increase milk and meat production. After all, the rumen is an effective digester, and a fair amount of the energy which is contained in the fodder goes to waste in the form of methane. Non-toxic antibiotics, specific for the methane-producing part of the bacterial population, could be of great significance.

In view of the rapidly increasing knowledge about the chemistry of the sites that make bacteria adhere to mucous membranes in the body, it is also reasonable to speculate about inoculation at birth with micro-organisms tailor-made to produce essential amino acids, to decompose undesirable compounds such as fungal toxins and perhaps even to fix nitrogen.

4. The prevention of post-harvest losses.

More than 60% of all fruit, vegetables and gr n undergoes some microbial spoilage. In industrialized countries this can be counteracted by the expenditure of energy for drying, heating, rapid transport, maintenance of "cold chains", and the production and use of suitable packing materials and antimicrobial agents. Examples of the latter are blasticidin S, kasugamycin, validamycin and polyoxins. Agents used in medicine are avoided in food production and preservation in view of the increased risk for the development of disease agents resistant to therapy. However, there is no lack of compounds that could be considered for non-medical uses. About 4000 antibiotics are known, but only about 40 are widely used. Finally it should perhaps be pointed out that the pressure to hold down food prices by economies of scale has led to very close contacts between farming and food processing, an important factor for product quality. It goes without saying that this capital-intensive model is not easy to adopt in warm climates where transports are slow, farms small and underemployment widespread.

Poor countries have every reason to exploit the potential of applied microbiology, which for instance offers many silage methods that convert labile organic material to stable and nutritious fodder. There are also many food fermentation processes that save energy by reducing boiling times, remove undesirable components, preserve the product and improve its nutrition value and palatability. Such techniques, which normally depend on natural populations of microorganisms, have long played a significant role particularly in Southeast Asia. However, some cases of food poisoning, and a considerable variability in many of the products, indicates that the production and distribution of safe and potent inocula might eventuallly play the same role as the starters now used for making cheese, yoghurt and wine. Controlled rapid food fermentations that would make it possible to avoid the salting procedures which tend to make certain foods unpalatable to children could for instance have a significant nutritional impact. Many other food technologies, briefly mentioned in a subsequent chapter (I) on industrial practices, might in addition be converted into appropriate technologies for poor countries, even if they are currently focused on real or perceived needs in the industrialized parts of the world.

5. Microbial protein as a nutrient.

Some of the products discussed above belong to the category MBP (Microbial Biomass Protein), since they contain substantial amounts of the substrate. In SCP (Single Cell Protein), on the other hand, the microorganisms dominate completely over the substrate, from which they are normally removed. In this case the substrate can be liquid or gaseous n-alkanes derived from oil, or it can be simple sugars and alcohols or even carbon dioxide and hydrogen. Normally, pure cultures of bacteria, yeast or algae are used in such processes, but defined mixed cultures occasionally give better yields.

The SCP area has been under active study for more than a quarter of a century, and yeast protein has been used to a varying degree in foods and fodders for a long time. Until the oil crisis in 1973 there was widespread hope that the microbial conversion of hydrocarbons to protein would satisfy any conceivable future needs of an expanding world population. In some oil-producing countries this substrate still holds attraction as a component in the type of integrated fodder/food production systems that might economize water use and increase self-sufficiency in eggs, poultry, veal and beef. However, in other parts of the world the emphasis now seems to be on starch, sugars and alcohol as substrates, partly as a result of the oil crisis, but also as a consequence of the fate of some major n-alcane based factories in Japan and Italy. In some of those cases the product testing might not have been quite adequate, but in others the cancellation of the projects was obviously more political than scientific in nature. In fact, few food products marketed today meet the rigorous product quality definitions that are applied even to animal feed SCP. Against this background it is reasonable to assume that SCP based on alcanes might make a comeback if the substrate does not become too scarce. This possibility obviously was one consideration when several companies decided to consider methane as an alternative. Methane can be used directly by some microorganisms, and can also be converted chemically into methanol which can be made very pure, and is a good carbon source for some bacteria and yeasts. In fact, a commercial-scale plant, with a design capacity of 50,000 to 70,000 tons per annum, is now being successfully operated by ICI in the UK.

There is little doubt that SCP from a variety of abundant substrates will be a major fodder source in the future. Since many microorganisms can be made to produce oil and starch in addition to protein, it may, in fact, be permissible to say that the limits to the world's food supply are political-economic and not technical. It is even possible to visualize floating fermentation units produced in the industrialized world and towed to locations where the substrate (e.g. flared methane) is abundant. From a purely technical point of view the oil-producing countries, as well as many industrialized nations, could drastically reduce their drain on the world's main ingredients of fodder preparations: soya proteins and fish meal. The former is produced mainly in the USA and Brazil, which underlines a geographical imbalance that compounds the geopolitical problems embedded in the location of the major grain-producing areas. Fish meal, on the other hand, is a protein source which is derived from a world catch that can hardly be increased, and which must also increasingly be diverted to human consumption.

SCP is already an important option for the USSR and Eastern Europe, and price increases in soy protein are expected when the cultivation is pushed into marginal areas and the other important soybean product, oil, meets growing competition from palm oil and other vegetable oils. This is likely to accelerate SCP production in many other parts of the world. From an initial focus on fodder use SCP is likely to find its way gradually into foods -- possibly by way of meat substitutes, an area where food technology has made great strides in the last decade.

6. Alternative scenarios for issues and priorities

Positive

- The food industry becomes increasingly science-oriented and advances in design engineering and chemical technology open the way to cheap and tasty meat substitutes from vegetable and microbial protein.

- Intergovernmental agreements on sugar and starch price policies help many developing countries and simplify investment planning for the fermentation industry.

Negative

- Imported technologies accelerate cash crop production and counteract food fermentations, biological control approaches and other contributions to self-reliance.

- Food industries become oriented towards labour-management relations and adjustments to a growing control bureaucracy.

- The trade orientation of established food industries (brewing, dairy, meat production) dampens impacts of modern bioengineering.

- Microbiological approaches to post-harvest crop protection become increasingly important, and food fermentations reach greater geographic spread.

- International agreement on production systems for a small number of essential and therefore low-priced generic products influences planning in the food and pharmaceutical industries.

- Rapid growth in control regulations and non-tariff barriers causes decision-makers to lose touch with the global realities.

- Convenience foods penetrate markets where the social system is not ready for the negative effects of status products and women entering the labour market.

- The gap between overfed and starving increases.

- Devaluation of human life becomes pronounced and "triage" or "lifeboat" philosophy is accepted as unavoidable.

H. HEALTH

> Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity.
> · Preamble to the WHO Constitution

1. Planning for well-being in developing countries

Health is the result of many interacting factors. It for instance requires an environment that meets certain minimal standards with regard to pollution levels. There must be enough fuel to boil water and prepare food, and to keep a shelter heated and lighted. Finally the nutritional status must be adequate to maintain the body's defence mechanisms against stress and infections. Obviously we are talking about the sum total of the possible improvements mentioned in the earlier chapters, even though for instance sewage and waste management were discussed more from the point of view of energy and fertilizer supply than as a fundamental element in sanitation. However, the latter is essential, for instance to the control of the intestinal parasites that consume much of the food ingested. This is of course also wasted by diarrhoeas and febrile diseases. Consequently, the nutritional status easily becomes inadequate not only to support the body's defence mechanisms against viral and protozoal diseases, but also to maintain a reasonable working capacity. In addition, cases of acquired mental retardation as well as chronic diseases leading to blindness and other severe handicaps put a heavy burden on society.

By the year 2000 Mexico City is projected to have more than 30 million people, Calcutta will approach 20 million and Greater Bombay, Greater Cairo, Jakarta and Seoul are all expected to be in the 15 - 20 million range. The majority of people in such towns will live in slums with extreme pressures on sanitation, water supplies and health care. Food, water and health problems are likely to be even worse in rural areas, since the most dynamic inhabitants tend to migrate to the cities and the number of physicians is extremely low. For a country such as India, it has been stated that 80% of the population is rural, but that four-fifths of the physicians live in the cities. The situation thus makes one wonder whether the health care delivery model of the rich countries is appropriate for the poor ones. They might for instance need more advanced teaching aids for a large body of para-medical personnel than industrialized nations. Also the need might be greater for cheaper and more reliable diagnostic kits. There is obviously much scope for innovative industrial efforts in the health care field.

The industrialized countries are characterized by a high level of specialization, making a microbiologist an expert in just one field (human pathogens, animal infections, plant diseases, soil science, dairy microbiology etc.). There is consequently no overview of the vicious circle of poverty - malnutrition - infection, as well as the multidisciplinary background which a tropical paramedic must have - sanitary engineering, food preservation, insect control, etc. - in order to come to grips with the diseases. Obviously, we face a back-up need of unprecedented magnitude.

2. A challenge to the instrument industry

The industrialized countries have an infrastructure which provides laboratory assistants to interpret visual observations and to translate instrument readings into guidance for therapy. They have service engineers to repair faulty equipment and specialists to evaluate obscure situations. Social and technical innovations are obviously needed to compensate for the lack of this support in the developing countries. Modular design and self-diagnosing circuits should for instance be standard in mass-produced electronic instruments. Mobile clinics and vaccination teams should be provided not only with robust equipment but also with communication facilities for efficient data handling and expert support.

It is certainly true that most robots for staining or serological screening, and the various devices that are now available for electro-physiological testing, rapidly become useless in the humid tropics. This however does not illustrate insuperable barriers of a technical nature but rather the fact that the instrument makers have not felt the need to make use of the materials and engineering principles that are well known to the makers of military equipment.

Hopefully, the fact that enzyme engineering is now in the focus of interest among medical engineers may help to stimulate instrument makers to develop more reliable, robust and easy-to-use equipment. The medical engineers are for instance experimenting with microencapsulated (active compounds enclosed in minute capsules made of semi-permeable materials) or membrane-bound enzymes and adsorbants that might be used in compact, portable detoxifying devices, shunted into the blood circulation as an alternative to the cumbersome dialysis units now used in the treatment of kidney diseases. Such "artificial organs", that might eventually also incorporate monoclonal antibodies and other highly specific agents, would have to combine cheapness with a very high level of reliability. The experience gained in their design might be of great significance applied to the needs of developing countries.

Biomolecular engineering indicates a number of other opportunities to make some of the shortcuts earlier indicated. Highly specific diagnostic kits making use of monoclonal antibodies are already being test marketed. Such antibodies can for instance be labelled with enzymes that make them easy to detect, or they might be attached to tiny magnetic particles making it easy to "fish out" specific pathogens from fecal matter or from suspected water and food. Novel approaches to mass health screening, incorporating analyses of nutritional status, can now also provide a baseline for broad public health strategies such as vaccination campaigns.

3. Trends in vaccine production.

In most cases such campaigns need not lack adequate quantities of efficient vaccines. In recent years bioengineering has in fact made great strides in the large-scale production of virus vaccines, first from cells derived from animal tissue and then from human cell lines growing on inert materials, – either on stationary media or on particles suspended in appropriate liquid media. Such media contain high concentrations of amino acids and proteins which are quite expensive. However, many of the former can now be produced very efficiently in their appropriate, optically active, form with the aid of immobilized enzymes, and genetic engineers have been able to design bacteria that can produce proteins similar to those found in tissue culture media.

The efficiency of the Japanese enzymatic technique for converting the mixture of amino acid forms that is derived from chemical synthesis, into the desirable active form, is shown by the fact that a reactor with a volume of one cubic meter has produced 500 kg of a particular amino acid per day. The continuous process ran for more than two months before the activity had dropped to half. In one case, where the feedstock was converted to 99%, one ton of immobilized cells of E coli produced 1700 kg every 24 hours.

The productivity of bacteria engineered to make proteins characteristic of higher animals is also impressive, for instance 70, 000 molecules of chicken ovalbumin per E coli cell.

However, the question is whether there is much reason to speculate about cheaper tissue culture media. After all, it is now possible to sidestep the tissue altogether and to engineer bacteria that produce viral, bacterial and parasitic antigens which can be used either as sub-unit vaccines or as diagnostic reagents. Many of those products are now not only expensive but also hazardous to manufacture, so their production via bacterial fermentations will certainly soon be exploited. This seems particularly likely in the case of small molecules that can be fairly easily isolated and analyzed. An example might be an antigen from the microorganism which causes cholera. It seems to induce resistance to this dreaded disease and may also be active against certain other pathogens which cause diarrhoea.

Diarrhoea is a common affliction in many developing countries. There are areas where children, on average, suffer from this condition two months out of twelve, serving as a reminder of the size of the reservoir of pathogens that an epidemologist must contain and reduce. But many new approaches are now available, for instance enzymes that can chop off immunologically active side chains from ballast material and toxic components. Having obtained such fragments an interesting possibility is then to use them for blocking the sites where a pathogen normally adheres to the body, and another is to make them antigenic by attachment to suitable carrier molecules. It should also be noted that the microbial geneticist can now suggest a number of different routes leading to attenuated but live vaccines that can be used safely against diseases such as typhoid, dysentery and cholera.

4. Genetic engineering for drug production.

Genetic engineering might also influence the fight against infectious diseases by switching the production of certain antibiotics and specific enzyme inhibitors of medical interest from fungi, which may be difficult to grow, over to bacteria that are easy to handle. Also precise modifications will certainly be made in the genetic codes which determine the structure of such therapeutic agents. Their toxicity might thus be reduced and their therapeutic efficiency increased. Finally, the significance of antiviral agents such as interferon, made in large quantities by fermentation techniques, should not be underestimated. The same is true for monospecific antibodies that eventually may become useful as homing devices for powerful drugs active against tumours or parasites.

To what extent the efforts mentioned above will be focused on health problems in poor countries is however difficult to say. The fact that a new antibiotic, avermectin, was developed for pets rather than man gives some food for thought. It is effective against filariasis in dogs, but has great potential as a treatment for river blindness.

Microbial agents are also known that are active antitumour agents; others show promise in the treatment of gastric ulcers, blood clots, hypertension and alcohol addiction; but in all such cases the development is apt to be slow in view of the stringent testing regulations in most countries.

Considering their relatively simple structure and potential medical usefulness, it is natural that the polypeptide hormones attracted attention as soon as their human genes could be modified so as to fit into the metabolic machinery of the genetic engineer's workhorse: E coli. Chemically synthesized genes were first employed to make somatostatin, but subsequently also thymosin-alpha-1 hormone and the two building blocks of insulin were made in this way. Synthetic information molecules have also been used as dies for the enzymatic synthesis of the genes that code for human growth hormone and pro-insulin. Using such dies, several different types of interferon have now been made, as well as certain surface antigens of viruses. In one case (hepatitis B) the genetic engineers have been able not only to make the surface antigen but also the core compound.

Several other medically important drugs have also been made with the aid of genetically modified microorganisms, and many others are in advanced stages of development (human alpha, beta and gamma globulins and certain coagulation factors as well as an enzyme that dissolves blood clots, plus a couple of hormones: chorionic gonadotropin and somatomammotropin). A combination of genetic manipulation with monoclonal antibody techniques may eventually also open a new approach to the efficient production of antibodies suitable for the diagnosis and treatment of specific diseases.

The advances in genetic engineering are thus impressive, but chemical synthesis of the smaller polypeptide hormones offers a competitive approach and, in the long run, inducers of natural interferon production in the body may be preferred to the artificially reproduced molecule. Finally, it should be mentioned that enzyme engineering occasionally might make a natural product very competitive. An interesting example is bovine insulin, extracted from slaughterhouse glands. This can now be made "human" by the simple replacement of one amino acid.

However, there is little doubt that various new techniques that make microorganisms secrete the desired product, and thus circumvent the need to separate it from the cell mass, may give genetic engineering an edge. Further, the use of manipulated yeast cells makes it reasonable to hope for production systems that will be both stable and capable of manufacturing many of the biologically important polypeptides that have specific carbohydrate residues attached.

5. The potential of plant tissue culture.

Besides using genetically manipulated microorganisms, the pharmaceutical industry will certainly also use microbiological techniques in the handling of plant tissue culture for the production of drugs with high added value and low volume. Approximately 25% of prescription drugs come from the plant kingdom, often from large plantations which are subject to political instability, bad weather and a wide spectrum of infestations. The need to have a constant supply, and the fact that synthesis via genetically modified microorganisms is probably quite a long way off (plant drugs are normally the end products of very complex pathways), explains the efforts that are now going into plant tissue culture. As a consequence of improvements in the media (defined composition, cheaper chemicals) and the cultivation techniques (immobilized cells,airlift reactors) this has advanced greatly in recent years. In fact, diagnostic enzymes, like phosphodiesterase from tobacco, are now sold commercially, and some alkalcids and the heart medicine digoxin have been produced in good yields. In many cases (anthraquinones, ajuralacine and serpentine, diosgenin, ginseng saponins and nicotine) levels have actually been achieved which exceed those observed in plants. It should be mentioned that diosgenin is a precursor to the drugs used in contraceptive pills - a product of obvious relevance to developing countries.

In fact, careful selection and manipulation can now often lead to results that make it reasonable to analyze plant tissue cultures not only for alkaloids and cardiac glycosides, but also for antibacterial and antiviral agents, for enzyme inhibitors and other substances active against leukemia, and for opiates, hormones and steroids. The fact that only some 2500 of the 250,000 higher plant species on earth have been subjected to organized pharmacological screening points at a great untapped resource. However, it remains to be seen if it will be the medically important drugs that will have the greatest impact, or if it will be the insecticides, plant hormones, oils, aromas, flavour pigments and perfumes that have also been reported from plant cell cultures. Much depends on the costs of efficacy and regulatory testing which - in the pharmacological field - often amount to 80% of development costs.

6. The use of enzyme engineering for the development of new drugs

Obviously genetic engineering and cultivation technology are likely to contribute greatly to the development of new drugs, but enzyme engineering will also help, for instance by exposing the basic antibiotic skeletons to chemical modifications (cf. the use of immobilized enzymes to make semi-synthetic penicillins) or by making hormones from appropriate raw materials (cf. the use of immobilized cells for converting cortisol to prednisolone). Since many of the latter may be produced in developing countries their scientists should consider the economic returns of enzyme engineering used for improving extraction yields and for upgrading natural products.

7. Alternative scenarios for issues and priorities.

Positive

- Against the background of the successes in the smallpox and rinderpest eradication campaigns and the breakthroughs in biological control, immunology and genetic engineering, the WHO diarrhoeal and tropical disease programmes are greatly expanded.

- There is international coordination of regulatory activities aimed at accelerating the spread of the most desirable medical innovations.

- There are coordinated efforts to develop equipment specially designed for use by developing countries

- Natural environments are systematically tapped for new drugs.

Negative

- Planning of medical aid continues to be based on a supposed link between missionary spirit and competence.

- Health care delivery systems continue to be modelled for large-scale establishments and advanced equipment. Expensive drugs and artificial organs are emphasized in the application of the advances in biomolecular engineering.

- Polarization intensifies between a medical elite with imported values and paramedical personnel.

- The weak infrastructures in developing countries are unable to fulfil expectations for rapid progress.

- Management of slum epidemics and parasitic diseases becomes increasingly difficult.

- A "triage" or "lifeboat" philosophy is accepted as unavoidable.

I. INDUSTRY - OPPORTUNITIES AND PITFALLS

1. The present and future size of the fermentation industry.

All the previous chapters have given examples of industrial uses of applied microbiology and biomolecular engineering, but the expected volume of the activities has only been indicated in very general terms. We are obviously discussing an industrial activity that is already large, in terms of both the companies involved and the tonnages produced. A 1977 review noted that 145 companies worldwide were using fermentation for the production of fine chemicals and therapeutic substances, and 85 companies manufactured yeast for feed and food purposes. In 1979 the world saw the production of some 80 million tons of beer, 13.5 million tons of cheese and 11 million tons of baker's yeast, besides 300,000 tonnes of citric acid and 10,000 tonnes of benzyl penicillin.

Some years ago the leading country in fermentation technology, Japan, used microbiological processes in industries with annual sales around 10 billion US dollars. The products, which contributed 5% to the government's tax incomes, included some 200,000 tons of glutamic acid and 20,000 tons of lysine, important food and fodder supplements.

A fertile soil for the recent advances in biomolecular engineering obviously exists in many countries, but to what extent will it be responsive?

To answer this question it is of interest to cite a few figures from the report, "The impact of genetics: applications to microorganisms, animals and plants", recently published by the Congressional Office of Technology Assessment in Washington. This does not visualize any direct replacement of any current industry within the next 20 years, but estimates that the overall annual economic impact of genetic engineering on the chemical industry will be measured in billions of dollars. It expects that medicines based on genetic engineering will become important, led by interferon with a market value of 1400 million US dollars, followed by synthetic antibiotics (1100 million US$), vaccines (260 million US$), human insulin (235 million US$), and hormones (100 million US$).

The report expresses the view that the chemical industry will be influenced particularly with regard to the use of renewable resources, physically milder conditions, one-step production methods and decreased pollution. The last aspect may be of particular importance in view of the fact that the US Environmental Protection Agency has estimated that the total cost for pollution control between 1977 and 1986 will be more than 360 billion dollars. About 7% of those costs will be borne directly by the chemical and allied industries, and this means that the cleaner processes and better waste treatment systems that are offered by genetic engineering may save very large sums of money. However, it is necessary to note that fermentation industries may themselves generate environmental problems of considerable magnitude. The effluent from a single brewery may for instance amount to 10,000 m^3 per day, and this pollutes as much as the sewage from a population of some 200,000 people. However, unlike much of the waste from traditional chemical industries, the waste from bioindustries is degradable and can also often, in principle, be managed by microbiological techniques that turn it into a resource. Also, many production processes can be modified so as to reduce the effluent problems significantly. In some places in Japan molasses has for instance been replaced by acetic acid as a nutrient for yeast and for monosodium glutamate production.

The impact of biomolecular engineering on the production of high value/low volume products is fairly easy to predict, but its influence on the heavy chemical industry is more difficult to estimate.

A group of experts from Massachusetts Institute of Technology and representatives from a firm specializing in genetic engineering, however, agreed that the production of the following chemicals might be influenced by genetic engineering in the course of the next twenty years: acetic acid, acrylic acid, adipic acid, ethanol, ethylene glycol, ethylene oxide, glycerol and propylene glycol.

2. The competition between chemical and biological processes.

Except where strategic considerations make it natural to subsidize such fermentation products as ethanol, acetic acid, acetone, butanol, isopropanol and glycerol, the petrochemical processes are difficult to beat. They use feedstocks that are easy to store and transport, they are flexible and well-understood, they normally give higher carbon yields than fermentations, and finally they are suitable for large-scale cost-cutting operations. The fermentation advocate will have to live with the fact that some things are better done by non-microbiological methods, and that the potential of bioengineering will be demonstrated mainly in the production of complex substances and special chemicals, for instance the optically active molecules that might be needed as polymer precursors.

This being said, however, it should be noted that DNA-hybrid techniques have already been applied to the enzymatic oxidation of ethylene and propylene and to the production of industrial alcohol, and that those approaches have shown enough promise to initiate pilot plant experiments. A very striking development is also the fact that the genome of microorganisms that convert methanol and ammonia to cell mass has recently been successfully manipulated towards improved ammonia utilization. Such bacteria, with their unique potential for utilizing simple molecules that can be derived from a wide range of raw materials, obviously now enter the scene as producers of a wide variety of chemicals.

3. Bioengineering and the food industry.

With regard to complex fermentation products, bioengineering will play an increasingly important role in the manufacturing of such products as beer and cheese. In both cases continuous processes have been developed and microbial enzymes, including replacements of malt for brewing, are finding increased use. New products like non-alcoholic beer, flavoured yoghurts, dairy products free from lactose (of which some people are intolerant) and milk with improved keeping qualities have appeared on the market. In the baking industry, fungal enzymes can be used to increase the level of fermentable sugar and make the dough easier to work. Additional gains are increased volume and a better crust on the bread. Microbial rennet is used on a large scale for cheese making, and selected proteolytic enzymes are used to modify the functional properties of animal and plant protein. Other types of enzymes are used to increase the viscosity of convenience foods, to remove cloudiness from wine and bitterness from fruit juices, to peel tomatoes, to improve the keeping qualities of egg products, etc. A much better use of the waste materials from slaughterhouses and fish processing industries is another natural consequence of developments in enzyme engineering. Finally, it should be noted that the food industry is showing great interest in plant tissue culture as a potential source of flavours, pigments and essential oils; and in microbial polysaccharides that might become useful in the formulation of various convenience foods. The sugar industry is certainly aware of the fact that sugar is the dominating cost factor in plant tissue culture media. It is also the normal raw material for the production of microbial polysaccharides.

As indicated previously, genetic engineering may also come to play a role in many of those fields, and proteins with important functional properties may soon be produced by genetically modified microorganisms. The significance of microbiologically produced essential amino acids and vitamins is so obvious that it needs no elaboration.

4. Bioengineering and substitutions.

For a long time to come the dominating carbon source for the majority of fermentations will certainly be sugar, a commodity traditionally subject to great price fluctuations which make planning equally difficult for the manager of a fermentation plant and for the minister of finance in a country that depends on sugar export.

Two adjacent notices in the Financial Times for April 10th, 1981, illustrate the problems in a nutshell. One notice observed that world sugar values on April 9th fell to their lowest level for a 12-month period. The decline was clearly related to EEC subsidies to white sugar export, but it was also noted that US sugar consumption had fallen sharply in 1980. The other notice referred to the Jamaican government's willingness to accept a proposal from a UK group to take over the island's ailing sugar industry for a seven-year period. The proposal pertained to the state-owned sugar factories, which produce 75% of the island's raw sugar - the same factories, in fact, that were run by a UK group before being taken over by the government eight years ago.

Since industrial sweeteners in beverages, foods, sweets etc. represent a substantial fraction of the sugar consumption in technically advanced countries, it is reasonable to assume that the switch in raw materials from cane sugar (sucrose) to starch has been an important factor in the reduced US consumption of sugar. Starch is a surplus commodity in the USA, and it is easily converted by microbial enzymes to glucose. This only has 40% of the sweetness of sucrose but can reach the sweetness level of the latter if it is partly converted to fructose, which is 120% to 180% sweeter than sucrose. This is done with immobilized enzymes, so it is reasonable to say that enzyme engineering has already radically changed the market in the US for high-fructose syrups. In fact 30% of the market had been taken over two years ago, and the technique now forms the basis for a production of more than 2 million tons of carbohydrate sweetener per year. By 1985 the market is expected to have grown to four million tons. The immobilized biocatalyst mentioned can also be combined with the enzymes that attack the sugar in whey, opening a way to convert this waste material into still more sweet syrup.

Genetic engineering is soon likely to be a factor in the sweetener industry. The reason is that a natural product, which is more than a thousand times sweeter than sugar, can now be produced in bacteria rather than from a tropical plant. This is yet another warning to countries that have not diversified or upgraded their crops in order to achieve a reasonable degree of self-reliance.

However, it must be emphasized that a "quantum jump" in bioindustrial activities needs a solid platform for takeoff. Fermentations for high-value products may require an infrastructure that few developing countries have. On the other hand their local markets for some products are so large that a strong basis for later foreign sales might be developed. However, the products must then have such a quality that they can meet stringent regulatory requirements.

5. Alternative scenarios of issues and priorities

Positive

- A systematic development of process engineering and downstream processing, coupled with high-level advice, balances the "overselling" tendencies and the neglect of industrial hazards that might be pitfalls for countries that enter the field of applied microbiology quickly.

- Methanol as a substrate and chemical feedstock "node", attracts increasing attention from genetic engineers.

- Microbial polymers become increasingly important.

- Greenhouse and digestion technology, as well as the production of plantlets, starters and enzyme cartridges, attract industrial attention.

Negative

- Unwarranted expectations of quick returns from investments in biomolecular engineering, coupled with neglect of infrastructure needs, cause severe repercussions.

- The situation with regard to industrial sweeteners is repeated with other substitutions, having a negative impact on countries oriented towards raw material export.

J. THE NEED FOR NATIONAL BIORESOURCE POLICIES IN DEVELOPING COUNTRIES

In the preceeding chapters, various basic needs have been selected to illustrate the wide spectrum of industrial activities which are relevant to developing countries and which will be stimulated by the recent advances in microbial genetics, enzyme engineering and fermentation technology. This has been done in order to counter the common misconception that the main industrial impact areas of applied microbiology and bioengineering are in the pharmaceutical and food industries. Those are certainly important, but if long-range planning for education does not take a broader view, costly errors are likely.

In industrial countries with effective information networks, warning signals come early and trigger c rrective measures. In developing countries, on the other hand, strategic decisions are more onerous and therefore call for efforts tructures that compensate for a weak infrastructure base.

The. e is certainly no lack of abstract journals and relevant review articles and reports, and if one adds the growing number of data bases it becomes obvious that the bottleneck is the process of sifting out the information needed for decision making in developing countries. If this is just a passive operation it means that a country's selective advantage is easily missed and that a situation of perpetual dependence is maintained. Advances must be weighed in the context of the strengths and weaknesses of the country in question, and the consequences of alternative actions must be evaluated on the basis of the experience gained in areas with a similar profile of needs and resources. This of course boils down to the need for national bioresource policies, where the long-range fuel-food equation is solved in such a way that the environment is protected and the economic situation improved. In this connection the choice of domains for industrial activity are of crucial importance. In most instances the upgrading of local resources is then an obvious priority, but there are other cases where efforts aimed at the improvement of the primary productivity should take precedence.

To order a genetically engineered microorganism from one of the specialized firms that have mushroomed in recent years is one small step which a developing country might wish to make in the direction of diversification and upgrading of its agricultural products. However, the fact that the appropriate laboratories, pilot plants and factories can now, in principle, be ordered "from the shelf" does not help much if the buyer does not appreciate that biological feedstocks are complex and subject to seasonal variations and to decay processes that influence quality; or that industrial processes normally require good water quality and a reliable supply of power and of cooling medium. Finally it must be noted that the "downstream" processes are often as demanding as the fermentation process itself if toxic residues, antinutritional factors and undesirable flavours are to be eliminated from SCP or MBP products and fever-inducing molecules are to be safely removed from products made for injection.

The outcome of the competition between fermentation and chemical industries in various countries also depends on agroindustrial politics, on the marketing resources, on the capacity to integrate various energy and product streams and last, but not least, on the capacity to mobilize the appropriate "know-how". The latter might for instance concern alternative methods for recovering the product from the dilute solutions or suspensions that are common in fermentations. Frequently there is also the question of choosing between batch, batch-with-recycle or continuous cultivation techniques, and selecting methods that reduce the energy costs for sterilizing media and for stirring and aerating the cultures. Finally, it is important to balance the expenses for microprocessor control and advance computer programmes against labour costs.

Those comments boil down to the conclusion that the great opportunities introduced by genetic engineering must be supplemented with much process engineering before they can have a substantial general impact in developing countries. Until the unit process approach in bioengineering has reached the same level of sophistication as in chemical engineering, the writeoff time for the necessary equipment will be short and the capital costs high. They are also likely to remain high as long as our efforts to design fermentors of unconventional construction materials are low and the full impact of microelectronics is not realized. A mutually stimulating exchange between the developing countries and the industrialized countries in those fields, as well as innovations based on applied microbial ecology, would no doubt emerge through national "Biological Resource Development Teams". If they were supplied with mobile pilot plants they could help they were supplied with mobile pilot plants they could help many poor countries to make a flying start in bioconversion. They would provide a critically important training function at the same time as they would help to screen the microbial and plant kingdoms for new materials that could be exploited in the interest of the national economy.

Most chapters of this study give examples of the significance of activities that lie at the interface between different disciplines. This highlights one of the bottlenecks in our educational systems which, at the elementary level, rarely use microbiology as a gateway to the biology of nutrition, hygiene, ecology and the cycles in nature, and, at the university level, do not provide for the transdisciplinarity which clearly is the lifeblood of biomolecular engineering. Actually education may well prove to be the most critical determinant for future developments in the area covered by this study.

K. CONCLUDING REMARKS

The directions in which biomolecular engineering will develop depend on the balance between the pull of market forces and basic human needs on the one hand, and the push forces of inventions in biology and allied fields of engineering on the other.

In the industrialized countries the market forces are strong, and the infrastructure is capable of responding rapidly to the pull and push mechanism. However, the current concern with major problems related to energy choices, to the international monetary situation and to painful industrial adjustments, bring their planning horizons too close for coordinated efforts aimed at optimizing the social impact of microbial genetics, enzyme engineering and fermentation technology.

In the developing countries, market forces are weak and, in most cases, the infrastructure is too undifferentiated to permit an examination of any development alternatives other than economic growth driven by traditional industries. The latter are in fact often favoured to the point where the fundamental basis in agroforestry suffers.

The environmental concern in the industrialized countries, together with their long-range need to adjust their production processes towards renewable or truly unlimited resources, gives biomolecular engineering a unique strategic significance. This is underlined by the fact that its development can contribute significantly to the solution of many survival problems in developing countries. If those problems are not solved, all industrial planning is meaningless, since the resources which industry requires, physical as well as genetic, will be lost in catastrophic social turmoil. As Rector Soedjatmoko of the United Nations University expressed it in a recent speech, "equity is no longer merely a morally desirable objective but has, in the face of high costs of energy and its social, economic and ecological consequences, become a fundamental necessity".

An international mechanism to help developing countries to effectively utilize long-range potential of biomolecular engineering for industrial development, settlement planning and health, seen in the context of the global fuel, fertilizer and food problems, is obviously needed. Accordingly, an International Centre for Genetic Engineering and Biotechnology should be established. A detailed proposal 1/ for establishment of such a centre has been made by a mission of experts led by the author, after discussions with policy-makers, scientists and technologists in 16 developed and developing countries.

1/ The Establishment of an International Centre for Genetic Engineering and Bio-Technology (ICGEB), Report of a Group of Experts, UNIDO/IS.254