What Biotechnology Has In Store For Us[1]

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ABSTRACT. Biotechnology has initiated a profound revolution in science with enormous technological and social consequences. The next 15 to 20 years will see biotechnology playing an increasingly important role in society in general. It will have impacts in the areas of human health, animal nutrition and plant agriculture. There will be 9 billion people on earth in 2025, and all the resources associated with biotechnology will be needed to enhance life in the next century.

It is generally accepted that the first successes of biotechnology will be in the areas of human health. Recent discoveries suggest that during the next 15 to 20 years, biotechnology may shift the central thrust of medicine from treatment to prevention.

One of the first biotechnology products in the animal nutrition area that is likely to enjoy widespread use will be bovine somatotropin (BST) to help improve milk production and feed efficiency in dairy cows. Within the next decade, genetic engineering will also confer desirable properties on plants such as resistance to pests, pathogens and, finally, environmental stress.

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INTRODUCTION

What might the next 10-15 years of biotechnology have in store for society in general and especially in the field of agriculture? Such speculation always involves risk. The National Academy of Sciences and the National Research Council have made 5- and 10-year predictions since the mid-1930s which missed, among other things, antibiotics, nuclear energy, microprocessors, and molecular biology. However, speculation does serve a useful purpose: it enables the public to decide whether opening the door of biotechnology will lead to a wealth of new products or a mere handful of interesting curiosities.

This paper will discuss briefly some impacts of biotechnology on human health and on animal nutrition and health. It will then examine the potential impact of biotechnology and its intellectual core, molecular biology, on agriculture. It will also suggest some ways in which we can shift the central thrust of plant protection from treatment to prevention. Finally, it will comment on potential applications of biotechnology in the production of commodity chemicals and the potential use of biomass (e.g., plant wastes and cellulose) as a source of energy or raw materials.

DISCUSSION

BIOTECHNOLOGY. What is biotechnology? Why all the excitement? What does biotechnology have in store for science and society in general over the next 15 years? The term biotechnology will be used to denote these processes: 1) use of microorganisms, plant cells, animal cells, or parts of cells such as enzymes to produce commercial quantities of useful substances; 2) construction of microorganisms, cells, plants, or animals with useful traits by recombinant DNA techniques, cell fusion, and other methods besides traditional genetic breeding techniques; 3) the application of molecular biology to understanding how cells and organisms work, so that the activities of cells and organisms can be altered or repaired.

The "bio" part of biotechnology is principally molecular genetics, microbiology, biochemistry (especially protein chemistry), and immunology. The "technology" part is largely chemical engineering, especially fermentation engineering, separation technology, and the like. Although the "bio" part of biotechnology (i.e., the genetic engineering) receives greater public attention than chemical engineering, it is only a part of the total technological package. A good part of biotechnology, when it is practiced in industry, will be conducted by chemical engineers or, more precisely, by biochemical engineers experienced in fermentation, who know how to extract 1 kg of fastidiously pure protein from 100,000L of a dilute fermentation soup.

Although this paper focuses on the genetic engineering part of biotechnology, the scenarios that are outlined demand that biochemical engineering move forward at a rapid pace during the next 15 years.

HUMAN HEALTH. Most biotechnology research today is focused on human diseases. Hence, it is generally accepted that the first successes of biotechnology will be in producing proteins and peptides for human therapy. Molecular biologists have redesigned bacteria genetically to make substances native only to humans. Some well known products now being developed for applications to people include growth hormones, interferons (alpha, beta, gamma), interleukins, hormone-releasing factors, neuroactive peptides, and immunosuppressive factors.

Blood components also have been developed. These include clotting factors (for hemophilia), clot-dissolving factors (plasminogen activators — initially for treatment but eventually prophylaxis for strokes and heart attacks), human serum albumin, and anticoagulant factors.

Atriopeptigen is one of the most exciting new products under study. It was reported by a joint drug discovery team comprised of Washington University (St. Louis) and Monsanto Company scientists (Cole et al. 1984). The mammalian heart, strange to say, is a major endocrine organ. The cardiac atria can synthesize and release several biologically active peptides that exert profound effects on sodium excretion, urine volume, and smooth muscle tone and cause selective renal vasodilation.

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It is likely that by the end of the decade the atrial peptides and most of the other products mentioned will have been clinically evaluated in humans, and several will be in general use. However, for many of these powerful biologically active materials (e.g., peptides and proteins active at the picogram level), the most important therapeutic uses may not yet have been uncovered.

An important class of proteins and peptides that will also receive increasing attention during the next decade is broadly termed the neuropeptides. These include endorphins, enkephalins, gastrin, and others. A veritable arsenal of peptides and proteins produced by the human brain and by other organs have specific parts of the brain as their target and can profoundly alter pain, anger, appetite, satiety, sexuality, and many other elements of behavior. Unlike nerve transmitters such as acetylcholine, by which one cell affects its immediate neighbor cells, these neuropeptides affect millions of cells in specific areas of the brain and alter mood, desire, and motivation.

As soon as molecular biologists have produced adequate quantities of various neuropeptides, their effects and potential therapeutic uses will be analyzed by neurochemists and neurobiologists. It is likely that some will prove to be important therapeutic agents in themselves. It is almost certain that their study will lead us to an understanding of the molecular causes of and cures for crippling mental diseases such as schizophrenia, depression, and Alzheimer's disease, as well as causes of and cures for addiction.

Insights into deep-rooted causes of human cancer are also being gained. Potential for the disease appears to lurk within all of us; normal cellular genes can quickly be changed into cancer-causing agents known as oncogenes.

The development of vaccines and other therapies for the great parasitic plagues of mankind can also be anticipated. Malaria and the trypanosome-caused diseases (i.e., sleeping sickness and Chagas disease) are under surveillance and attack by molecular biologists and medical entomologists. Considerable progress is being made in the development of genetically engineered vaccines for malaria and for the trypanosome-caused diseases.

Novel strategies have been devised to overcome the ability of protozoan parasites to evade human immune defenses by secreting new coat proteins and other tricks. There is also the likely prospect that filariasis, schistosomiasis, and other diseases caused by parasitic worms will succumb to novel attack by molecular biologists and immunologists. Indeed, there is a reasonable likelihood that by 2000 A.D., these diseases will be controlled by a vaccination. Malaria is likely to be the first to succumb, then the trypanosomes and, finally and with difficulty, the worms (National Science Board 1985).

In addition, it is likely that other products of biotechnology will aid in providing early warning for various diseases. Scientists have succeeded in isolating specific DNA sequences that may predispose individuals to heart disease and emphysema, and are searching for genes that may predispose us to diabetes, allergies and peptic ulcers. Discoveries of this kind suggest that during the next 15 to 20 years, biotechnology may shift the central thrust of medicine from treatment to prevention.

Up to this point, the gene-splicing component of biotechnology has been emphasized. Yet many scientists believe that immunology will prove even more powerful in human therapy. As the comprehension of the immune system increases, the meaning of the "carbohydrate code" will be understood just as the nucleic acid and protein codes were unravelled. The biological significance of glycosylation, which is so widespread in eukaryotic proteins, will also be determined, as well as how therapeutic agents can be targeted to specific organs. Perhaps monoclonal antibodies will be used to clean up small numbers of cancer cells that often persist after surgery, chemotherapy, or radiation. It may also be possible to selectively control the immune response to transplanted kidney, heart, skin and liver so that they are not readily rejected. Diseases that will begin to succumb because of these advances include many kinds of cancers, autoimmune diseases, atherosclerosis, arthritis, and many others.

ANIMAL HEALTH AND NUTRITION. Since there may be 9 billion people on earth in 2025A.D., a number of strategies will be needed to enhance animal protein production. The opportunities in animal health and nutrition will be numerous. One of the first of the biotechnology products likely to enjoy widespread use will be bovine somatotropin. Extensive tests on dairy cows have already shown that bovine somatotropin (e.g., a peptide hormone) increases both milk production and feed efficiency (i.e., more milk from the same amount of feed). The development of vaccines produced by biotechnology for foot and mouth disease, scours, shipping fever, and other diseases of cattle and swine/can also be anticipated. As animals are raised under more crowded conditions, they will become more susceptible to disease. Genetic engineering of chickens, swine, and cattle is also a possibility. They will be born already vaccinated and resistant to diseases. It will also be possible to rapidly accelerate animal breeding for feed efficiency, disease resistance, and other desirable qualities (Olson 1986).

BIOTECHNOLOGY AND AGRICULTURE. Let us now turn to the potential impact of biotechnology on plant agriculture. Within the next decade or so, genetic engineering will confer desirable properties on plants such as resistance to environmental stress, pests, and pathogens (Ross 1984). There is reason to believe that temperature tolerance in various crops can be increased by the application of genetic engineering. Endowing crops with enhanced temperature tolerance will be a fantastic challenge. If the northern range of specific crops could be extended, it would be possible to increase the productivity of millions of hectares throughout the world. At these more northerly latitudes, crops are produced only one or two years out of four because of the cold. Increased drought tolerance in a crop would also be a major breakthrough because hitherto non-cultivated land could become productive for the first time. Crops could also be made resistant to heat stress.

Learning to control a storage protein gene could also lead to improved nutritional quality of seed grains. Similar work could serve to improve the nutritional quality of taro, manioc, and other root crops by increasing protein content and decreasing naturally occurring cyanide content.

Earlier maturation is another challenge. Plants that mature earlier will alter planting and harvest cycles and improve farm income. Herbicide resistance also promises to be of practical interest because it could couple cheap, safe, general herbicides with herbicide-resistant crops. There are also attractive opportunities to develop new crop plant varieties that keep top soil in place.

Crops Resistant to Insects: Prevention Instead of Treatment. Another prospect of plant biotechnology is to produce crop species that are resistant to insect attack. This would shift the central thrust of plant protection from treatment to prevention. What novel proteins and peptides should cotton, soybeans, and rice synthesize to provide protection against insect pests? What genes should be transplanted into a plant to endow the plant with resistance to insects?

The pests of insect pests may well hold a clue. What proteins and peptides do the viral, bacterial, fungal, and multicellular enemies of insects use to kill insect pests? Once the entomologist has identified those proteins and peptides, they become candidates for genetic engineering into crops. Needless to say, the proteins and peptides should enjoy some specificity and be insecticides and not be fatal to man. Also, they should not decrease crop yield. The introduction of those genes into crops offers the promise of insect resistance in key crops, a dream of the plant breeder.

Similar opportunities exist for fungicides and nematocides. What genes must be transferred to a plant to endow it with resistance to bacteria, fungi, insects, or nematodes? Here too the pests of pests may hold the clues. The pests of fungi, bacteria, and nematodes produce proteins, peptides, and other molecules that kill fungi, bacteria and nematodes.

How far are we from the prospect of genetically engineering a plant to resist insects? Three years ago I would have guessed 15 or 20 years. Recent dramatic advances in the transformation of plant cells, however, suggest a much shorter time frame. There has been great progress in the use of the microorganism, *Agrobacterium tumefaciens,* a soil bacterium that can introduce genetic information into plant cells while it creates tumors called crown gall tumors. The Ti plasmid carried in this bacterium has been engineered to disarm its tumorogenicity and yet maintain its ability to insert appropriate genes into plant cells in order to confer, for example, insect resistance to the cells.

It appears likely that the genetic engineering of plants will move forward rapidly, with crops engineered to be resistant to insects and other pests becoming available by the 1990s. Instead of treating crops with traditional pesticides, in some important cases it will be possible to endow the crop with pest resistance.

Gene Organization and Regulation in Plants. The application of genetic engineering in agriculture will have enormous impact in the future, but there are a number of impediments to rapid advancements in the field. One of the most serious problems is the lack of fundamental knowledge about gene organization and regulation in higher organisms such as plants. It is not known what turns genes on and off at specific times. Second, only about 25 of the many tens of thousands of genes in a higher plant cell have been characterized. Third, there is a large gap in the understanding of the basic biochemical mechanisms that regulate the growth, development, and reproduction of plants. In addition, the technology of tissue culture still requires study so that a greater number of economically important plants can be regenerated from either protoplast or cell systems. There is no doubt that the application of molecular biological approaches to plant research will expand knowledge about how genes are organized and regulated, both temporally as well as spatially, and will lead to considerable improvements in crop production.

An Enlarged Mission for Agriculture. The ability to genetically engineer plants will enlarge the mission of agriculture. Agriculture today focuses principally on food and fiber. But if plants can be genetically engineered to produce animal proteins, other prospects emerge. What if plants could produce human insulin or human blood factors for hemophilia or a vaccine? Perhaps the high-value-added crops of the 1990s will be plants that produce drugs for human diseases. Perhaps human insulin can be harvested from the "north forty" instead of from huge fermentation tanks of genetically engineered *E. coli.*

Another likely consequence of the genetic engineering of plants, although one that is further in the future, is the development of new crops designed not to produce food or fiber, but to produce feedstocks for the world's chemical industry. Unlike the other scenarios discussed, this one is not likely to occur on a broad scale until well after the turn of the century because of the continued availability of petrochemical feedstocks and methanol from natural gas. Indeed, the nearly universal consensus is that, contrary to earlier predictions, the world's oil and natural gas will last longer than had been predicted, certainly well into the fourth decade of the next century, if not longer. However, eventually these fossil fuels will be depleted, and renewable resources will be required.

Today latex from rubber plants, oil from palms and oil seeds, starch, molasses, sugar, cellulose, and lignin are the principal, moderately large, chemical feedstocks derived from agriculture. By the end of the century, however, crops will be developed that can produce other chemical feedstocks for the world's chemical industries. When that occurs, agriculture will have a broader market for its crops.

Genetically Engineered Soil Bacteria. A second aspect of biotechnology that is of potential importance to agriculture is the development of genetically engineered soil bacteria to enhance crop yields. Such genetically modified bacteria would be added to the soil or to seeds. Most plants live in loose association with microorganisms, forming biological partnerships. One partner is the familiar green plant such as the soybean or corn. The other tiny partners are the soil bacteria and fungi that may be intimately associated with the root system of the plant and act as "middle men" in transferring nutrients from the soil to the plant. Some of the organisms live near the roots of the plant; others actually invade the roots.

Bacteria that invade the roots of soybeans and "fix" nitrogen there to the benefit of the soybean plant are familiar examples. Much attention has been paid to these nitrogen-fixing soil bacteria that convert atmospheric nitrogen to ammonia and reduce the need for fertilizer. But there are numerous other opportunities for using soil microorganisms that could make obsolete some of today's pesticides and fertilizers. For example, increased attention is being paid to the genetic engineering of soil microbes to protect the roots of plants from insects, disease, and viral attack. One strategy is to develop microbes that secrete natural chemicals capable of killing pathogenic organisms and insects. Such a strategy could have considerable potential to protect plant roots with minimal environmental impact.

The use of genetically engineered microbes instead of chemicals or soil amendments for crop protection promises to be of great value in both highly mechanized, high-performance agriculture as well as in more labor-intensive agriculture. Microbial pesticides are particularly attractive because they will be less capital-intensive than many of the products traditionally used in agriculture. This will facilitate the introduction of such products into the agriculture of less developed countries. This biological approach to selectively controlling insects and other pests and to enhancing crop yields is likely to be a critical component of crop protection and yield enhancement in the future.

BIOTECHNOLOGY AND COMMODITY CHEMICALS TODAY. What can be said about the application of biotechnology to the production of large-volume, commodity chemicals? Can a biomass refinery be built that would take in millions of pounds of cellulosics like wood chips, corn stover, or bagasse and convert them to useful large-volume chemicals? The prevailing opinion today is that, although biomass conversion processes are now technically feasible, they are not economical for most countries. Biomass simply cannot compete as a petrochemical feedstock today nor with methanol from coal (U.S. Dept. of Commerce 1984).

By 2000 A.D., there will be biomass refineries in Brazil as well as other developing countries where there are special local opportunities to use cellulosic agricultural wastes such as bagasse, or where rapidly growing trees can be cultured and harvested. As time goes on, more and more biomass use will occur. As mentioned earlier, it is widely believed that most of the useful petroleum reserves on earth will be used up within 75 years, and that the world must learn to depend on renewable resources. In developing nations today, the use of agriculture for energy production must be second to food production. It is a delicate balancing act. Also, it is important to realize that more than a billion people today use firewood as their principal energy source.

In developed countries such as the United States, Western Europe, and Japan, there may be a new driving force for chemicals produced via biotechnology. By and large, such chemicals are environmentally safer to make. Molasses or starch is a far more attractive and less hazardous feedstock than are most chemical feedstocks based on petrochemicals. There may be an incentive to develop new processes for certain major bulk chemicals based on biotechnology. However, today the outcome is uncertain.

How readily are biotechnology products and biotechnology processes transferable to developing countries? Inventions do not improve the human condition until they are applied. It has not escaped notice that poliomyelitis still takes an enormous toll in many developing countries despite the existence of a reliable, one-time vaccination. However, here are some viewpoints to consider:

1) Almost any developing nation can make use of genetically engineered seeds and root-colonizing microbes. This kind of biological control of pests can enhance yield and eliminate importing petrochemically based agricultural chemicals.

2) A key need for the future is the development of agricultural testing stations where the use of products that enhance crop yields can be demonstrated and explained.

3) The introduction of disease-resistant and more efficient domestic animals is feasible.

4) New one-time vaccination processes, first for malaria, then for trypanosome-borne diseases, and then for the much tougher parasitic worms will be developed to meet the needs of the Third World.

5) Biotechnology is not highly capital-intensive, for the most part. Unlike many industrial processes requiring expensive feedstocks and sophisticated manufacturing processes, biotechnology can be practiced with limited resources. However, it does require an infrastructure, sources of equipment, repairs, and chemicals at about the same level as a medium sized Western hospital.

Despite the publicity that genetic engineering gets, its pending impact on society and its durability as a scientific tool in the service of humanity are underestimated. Indeed, it can be argued persuasively that genetic engineering may turn out to be the most significant scientific and technological discovery ever made.

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