Economic Aspects of Agricultural Biotechnology[1, 2]

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Ideas and words come in and out of fashion just like clothing, and in too many cases their real impact on the world, when viewed from a historical perspective, is not significantly greater than these other "fashions". But sometimes, seemingly by chance, the words and ideas that are in fashion match the real needs and opportunities of their time. At these times, progress far beyond the normal slope of forward movement can be achieved by forging real solutions from the tinsel of well-supported, *fashionable* ideas. I believe such a time is at hand for agricultural research. Four words or phrases currently very much in style are *biotechnology, economic development, new partnerships* and *excellence.* These mirror the unique opportunity that the agricultural research community has to address the economic chaos and depression that has seized American agriculture. Today I would like to address the real substance of these terms and the special way in which their meaning and potential for agriculture and agricultural research expand when they are viewed in the context of each other.

Biotechnology is often defined as the use of biological systems to produce substances and products too complex and expensive to make by other traditional chemical means. Biotechnology, as farming, is the husbandry of life forms to produce products. The concept of using the complex biological systems and mechanisms of nature's living organisms to produce products is as old as civilization itself. It is also very new and offers totally new ways of altering and improving these age-old systems. Both the new opportunities offered by biotechnology and its fundamental identity with agriculture suggest an enormous positive impact upon agriculture by this "fashionable" subject.

Before discussing the role of biotechnology in agriculture, it is useful to more closely examine the technology and the depth and breadth of its application in all areas of production and industry. The *new* biotechnology had its beginnings a little over a decade ago in research findings emanating from the study of molecular genetics and microbiology. The discovery of sequence-specific DNA cleavage enzymes known as restriction endonucleases and the perfection of other *in vitro* enzymatic means for the ligation or reconstruction of DNA molecules from isolated "restricted fragments" made possible specific, directed recombination between virtually any genetic information. Application of *recombinant genetics* first occurred in microbial systems where the existence of extrachromosomal genetic elements called plasmids, able to enter freely a variety of microorganisms and impart their genetic influence, allowed an easy means of transferring genes into these organisms. A range of isolated or *cloned* genes were introduced into bacteria and other microorganisms, generating recombinant microorganisms able to produce a variety of gene products.

Some of the products produced by recombinant microorganisms are today commercially available in the form of prescription pharmaceuticals. Human insulin, marketed by Eli Lilly for the treatment of diabetes, and human growth hormone, marketed by Genentech for the treatment of pituitary dwarfism, provide well-known examples of the first pharmaceutical products approved by the Food and Drug Administration. Other important new agents for the treatment of cancer, such as interferon, interleukin-2, and other lymphokines, are examples of

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[2]Edited text of an address given at the symposium.

the first harvest of microbial biotechnology. But because of the initial emphasis on pharmaceuticals — high profit margin products developed by an industry with a huge research budget able to support the initial technology development — many outside observers still see biotechnology as simply an exciting new means to produce new protein pharmaceuticals. Nothing could be further from reality.

A combination of the need for molecules far too complex to be produced by chemical synthesis, the impending decline in both the chemical feedstocks and fuels needed to drive the chemical industry, and increasing concern about the pollutants and by-products of production chemistry have prompted a dramatic turn from a basic *chemitechnology* to biotechnology. Already traditional biotechnology is used in such diverse arenas as minerals extraction in mining operations, for tertiary oil recovery, to produce more than 50 different complex chemicals, in the fermentation industry and in food processing, and in the pharmaceutical and vaccine industry. Methods and systems using industrial enzymes, produced by recombinant organisms, to catalyze complex multistep reactions for the synthesis of existing and new molecular products are at the pilot stage in many corporations throughout the world. Clearly, the age of biotechnology is upon us. But we are viewing only the very edge of change. In spite of the dramatic initiatives in the pharmaceutical and chemical industry, expert analysts, including the Office of Technology Assessment of the U.S. Congress, predict that the largest impact and increased proceeds from biotechnology will be in agriculture. Increased profits to the agricultural sector in excess of $100 billion per year are predicted within a decade as the direct result of biotechnological advances. Although I agree with the potential of these predictions, I am not quite so sure of their realization within this time period. The agenda for incorporating this new technology into the fabric of American agriculture is large and complex and defines the challenges facing our colleagues throughout the agricultural research, economic development, and extension communities. They are probably more exciting and more demanding than any of the challenges previously faced by these groups.

Life forms on earth may be divided among three general groups: microbes, plants, and animals. Since almost all systems presently using the new biotechnology are based on microbial systems and because broad-reaching, new methods of introducing cloned genes into plants and animals have been developed, it is clear that much of the future development of biotechnology will be in the realms of plants and animals. The use of plants and animals to produce products is agriculture. This is precisely the reason such a major impact by biotechnology on agriculture is predicted. Whereas chemical, pharmaceutical, and fermentation industries may move to production through microbial biotechnology, it is American agriculture and the American farmer, through their link to us in the agricultural research community, who will be called upon to become the plant and animal biotechnology industry of the future. What will this *industry* be like? What kinds and range of products will it produce? Our best guess as to the answers to these questions lies in the present laboratory successes in the fields of plant and animal recombinant genetics and biotechnology.

How may this *biotechnology* of animal and plant recombinant genetics affect agriculture and the American farmer? From my vantage point, I see two general areas of effect: 1) improvement in the production traits of existing plant and animal farm products by increasing production efficiency and lowering production costs to increase profits to a more reasonable level, and 2) providing totally new, high profit margin, non-food agricultural products. Clearly, the agenda for incorporation of biotechnology into production agriculture must address the first of these before moving to the second.

Several major changes in both production traits and the basic composition of animal and plant food products must be the first goal for the application of agricultural biotechnology by the agricultural research community. A decade ago many plant and animal geneticists, viewing the field of genetics from the point of view of population genetics or plant and animal breeding, believed that such a large number of specific genes contributed to the major production traits that genetic engineering approaches to animal and plant improvement, which allow transfer of only a few selected genes, could not be used effectively to improve the production efficiency of farm products. With an increased understanding of recombinant genetic techniques and an acceptance of their place in agricultural research, a new mode of genetic analysis and thinking has come to the fore. This analysis focuses upon the rate-determining steps in the complex biological processes that control the production traits of farm products. Examples of these traits are growth rates, growth efficiencies, reproduction effectiveness, and disease resistance characteristics.

This new approach within the agricultural research community has provided enormous impetus for the application of biotechnology in agriculture, and has provided specific targets for single-gene engineering. Examples of specific genes that regulate complex, multigene processes of crucial importance to animal agricultural production systems are the growth hormone gene in growth rate, feed efficiency, leanness and milk production; the baroola gene in reproduction rates; and specific lymphokine genes and histocompatibility genes in disease resistance. In plants, single genes have been identified that enhance the efficiency of nitrogen fixation in nitrogen-fixing plants. A small gene family has also been found that may allow plants that are not presently able to fix nitrogen to participate with nitrogen-fixing bacteria in a symbiosis. Plant molecular biologists have also isolated several bacterial genes that impart herbicide resistance to plants, potentially allowing better weed control in specific crop plant species. Because of the enormous wealth of genetic information available to the animal scientist from the huge national research effort in human health, more progress is being made in animal biotechnology at present, but the large recent emphasis on plant molecular biology is closing this gap.

Two specific genes, the animal growth hormone gene and the bacterial glyphasate resistance gene for plant herbicide resistance, which have been cloned and transferred, provide good examples of the direct application of genetic engineering to crop and livestock agriculture.

Experimental animals harboring the expressing growth hormone gene grow over 100% faster than control animals, are 30% more feed-efficient, and have far less body fat. Clearly, such traits conferred by a single genetic construction could dramatically improve the production characteristics in meat animals. This same gene also confers increases of up to 40% in milk production in lactating dairy cattle. Growth hormone, delivered by some means, will definitely have a major impact upon dairy and red meat production in the very near future. One of the major questions is the means by which this valuable gene product will be *delivered* to the farm livestock population. Several possibilities are presently under study. Since this first production-enhancing *biotech* agent may serve as the bellwether for future systems, it is important to look carefully at the alternatives available and the way in which each would affect agriculture as we now know it.

The protein hormone gene product of the growth hormone gene is being produced presently by several commercial groups through the use of a fermentation process employing growth hormone gene recombinant bacteria. When this protein hormone is administered to young, growing animals, substantial increases in growth rates and feed efficiencies are observed. These production improvements are far less, however, than those shown by transgenic animals that contain the expressing gene. Administration of this prepared hormone to lactating dairy cattle does show the full effects of milk production, boosting production 20 to 40%.

The advantages of this new production-enhancing agri-pharmaceutical to the farmer are obvious: increased product, improved efficiency, and a more effective and residue-free replacement for the anabolic steroids that are being maligned by consumer groups. But these advantages have a price. The cost of production and especially of purification of recombinant proteins from toxic bacterial suspensions is costly. A substantial portion of any increased profits to farmers will go toward paying these manufacturing costs as well as the marketing and research costs for the product. The companies producing these agents will also realize a profit margin substantially larger than the farmer ever sees on his products. Also, the costs to the farmer will not only be in dollars, but also in increased labor, since regular administration by injection or implantation will be required.

All of this suggests that a better mode of use of the growth hormone system may be through the permanent genetic alteration of farm livestock using animals that are transgenic for the expressing growth hormone gene, like the experimental animals described earlier. However, this system, along with its obvious advantages in effectiveness, cost, and profit share to the farmer, also has several drawbacks. Any change in the permanent genetic makeup of a living organism must be compatible with all aspects of the life cycle of the organism. While genetic engineering, which increases the level and the duration of growth hormone production within an animal, clearly and dramatically increases growth rate and feed efficiency, it also has some negative side effects on female reproductive performance. This should be of no great surprise to animal breeders since it has been known for a long time that an inverse relationship exists between prolonged, enhanced, growth, and attainment of sexual maturity. Although present experimental results suggest that transgenic animals with significantly enhanced growth rates and acceptable reproductive performance may be produced, it must be recognized that for permanently transgenic animals it will be impossible to maximize fully a single production trait by genetic engineering. Rather, a balance between all required traits must be achieved. This is a clear disadvantage compared to direct protein growth hormone administration for increased meat production, since by using direct protein administration, only animals destined for slaughter will be treated, and the effects on reproduction are of no concern. In dairy cattle, the relative advantage may not be quite so definite since some concern has been registered regarding effects on reproductive performance owing to long-term growth hormone administration. Delivery to the farmer is a second major practical disadvantage to the germline transgenic animal approach to production increases through the growth hormone system. Even if the most desired transgenic livestock could be produced by the agricultural research community, any reasonable estimate of the time necessary to reproduce and disseminate the animals to America's farmers and ranchers would suggest a time lag of a decade or more.

An alternative to both direct protein hormone delivery and the germline transgenic animal approach may be possible. Recent research in several molecular biology laboratories and at the Edison Animal Biotechnology Center in Ohio suggests that methods similar, but not identical, to human gene therapy, where specific genes may be introduced into populations of somatic cells in a young animal, creating a site of lifelong, but not germline, production of the gene product, are possible and practical for livestock applications. This system would allow designation of an animal for slaughter prior to gene administration, making any effects of the gene product on reproductive or other non-growth traits of little concern. Breeding animals and animals chosen as herd replacements would remain untreated. Since treatment would probably involve a single injection, this system would 1) provide rapid access to the farmer; 2) provide a good product for the agri-pharmaceutical industry, which would provide research investment for its development; and 3) because of low production costs and single dose administration, leave the major share of increased profits for the agricultural producer. Although this approach is presently at the early research stage, I feel that it has so many obvious advantages over other alternatives that it should receive major emphasis by our agricultural research community. I can assure you that it has this emphasis at the Edison Biotechnology Center.

This analysis of the potentially available methods of effecting the use of a production-enhancing system for agriculture is a very important exercise because, if this type of complex analysis is not carried out by the agricultural community and the research, teaching, and extension arms of agricultural units within our universities, decisions will be made by other groups. These, at worst, could create increased loss to the farmer and rancher through decreased prices for products and increased input costs. At best, they would leave only a small portion of the biotechnology profits for the producer. The role of the agricultural economist in this aspect of biotechnology is major. Those involved in technology development look to him/her for guidance in developing technologies that are really better for the farmer and rancher and not just exciting research projects for the researcher and high-profit products for the agri-pharmaceutical industry.

Although it is not my area of scientific specialization, it appears that biotechnology will have an impact on agriculture as large or larger than animal biotechnology. The best immediate example of its application will probably be in the development of herbicide-resistant plants. Already, glyphasate resistant tobacco plants are being tested by at least two plant biotechnology companies. The recent development of gene transfer in plants by clonal cell microinjection promises the rapid development of genetically altered, resistant cereal plants including corn, wheat, and rice. Through the use of specific resistant plant strains-herbicide pairs, weed control may soon be reduced to direct spraying. But, like animal biotechnology, we need to look at the optimal approaches, best uses, and desired targets for plant biotechnology from the point of view of the producer and not the biotechnology company.

In this age of biotechnology, many other factors are dramatically influencing, perhaps even shaking, the foundations of agriculture. Our choices for the application and use of biotechnology must take these into account. One of these factors is increased concern by consumers about the quality, nutritional value, and healthfulness of the food that they eat. As a member of the Committee on Technological Options to Improve Nutritional Attributes of Animal Products of the National Research Council, I am keenly aware of both the myth and reality surrounding nutritional and health deficiencies in the American diet. Whereas concerns over cholesterol, fats, and excessive calories are based upon sound data from agencies of the federal government, the dramatic movement away from specific products, such as red meat, in response to these concerns is wrong, ill-founded, and potentially nutritionally dangerous. But, since public attitudes often depend more on myth than truth, the agriculture industry, the agricultural university community, and especially those involved with livestock agriculture must act through information, education, and technology to make the consumer feel comfortable with a reasonable diet including a substantial proportion of each of the important food groups. Therefore, in addition to directing the powerful biotechnology toward increased production traits in animals and plants, we need to use this technology to improve the composition, healthfulness, and nutritional value of food products. Animal biotechnology must be addressed to decreasing the fat and caloric content of meat. For a variety of nutritional reasons, meat should be a major part of our diet, but it will remain so only if both meat composition and attitudes about this product change. Biotechnology can change meat composition; this change in composition, and the willingness of the livestock agriculture sector to work for this change, will go a long way toward changing attitudes.

Unfortunately, within the present national and world economy and because of worldwide governmental policies calling for the lowest prices possible for food, even technologies that allow farmers and ranchers to approach the upper limits of production efficiencies will not provide profit margins anywhere near those in other, more profitable, industries. The farmer pays $1,000 to $5,000 for a computer system that costs $200 to $850 to manufacture, and sells corn costing at best $1.75 a bushel to produce for $2.00 a bushel. The same higher profits are realized by the equipment manufacturers who supply his mechanized equipment, the builders who build his facilities, and the suppliers of his agri-chemicals. His profits from other cereal grains, meat, and all other food products are as low or lower than the corn example. Although this simplistic analysis of agricultural economics by an non-economist clearly misses many important factors influencing the farm economy today, I believe it may represent the base problem: farmers and ranchers are caught in a predetermined, low profit margin business. Until farmers begin to produce high profit margin, non-food products as part of their overall production, they are likely to remain economically depressed. An example of a product that has provided good income on small acreages in the past is tobacco. Although tobacco is not likely to remain a major product in the future, it represents the potential in agriculture for chemical or pharmaceutical bio-production, for tobacco is surely a drug. As only the closest observers of plant biotechnology know, the largest investors in the plant biotechnology industry are oil and specialty chemical companies. One of these companies is Lubrizol, which is a Cleveland-based, specialty lubricant manufacturer. This firm is heavily committed to plant biotechnology. Lubrizol appears to be orchestrating a long-range research and development program to produce sophisticated, high value lubricants in oil-producing plants such as soy bean, sunflower, and rape. This presents a great opportunity for the farmer. He may produce a specialty *chemical crop* destined for Lubrizol's processing plant. Of perhaps equal importance is the fact that such *chemical farming* may create new economic opportunity for non-farming, rural America. It seems unlikely that any national corporation will wish to take direct delivery for the unprocessed crop, but would either establish local pre-processing plants or create the opportunity for independent local companies to serve this function.

Clearly, biotechnology offers far more to agriculture than improved food-producing systems. Specialty plant oils are only one of many examples of what is beginning to be called *molecular farming*. Any reasonable analysis shows that microbial fermentation or mammalian cell culture production of protein or other bio-products is far less cost efficient than animal or plant production. For example, a dairy cow may produce close to 1 kg of a sterile protein, casein, at a cost of approximately $3.00, whereas microbial fermentation produces the same amount at a cost of over $500 and in a highly toxic bacterial medium that requires extensive purification. Most of our traditional farm species have been selected for their specific protein or bioproduct production capacity. Examples include chickens for their egg white ovalbumin protein and grains for their storage proteins, carbohydrates, and oils. We here today and the presently depressed farm sector have the bioproduction systems of the future. They are not in the hands of corporations or biotechnology companies; they are in our hands. We must work to keep them there and put them to use for agriculture and the good of all.

If molecular farming is to become a reality, a large investment will be required in very basic molecular biology and the application technologies needed to bring these production systems to the farm. Genes are composed of two distinct portions, the information-containing structural gene and the regulating or orchestrating genetic control sequences that direct gene expression to specific tissues at specific times in concert with the organism's physiology. By cloning both the structural genes of products to be produced by molecular farming and the regulational sequences to direct their production to dairy cows' mammary secretions, birds' egg white, or grains' storage proteins, creating gene chimeras between these elements, and introducing these gene chimeras into new strains of transgenic animals and plants, the agricultural research community may provide the farmers and ranchers of this country with the systems to produce a fair share of the future high profit margin, non-food products. The dramatic recent successes of the biotechnology industry indicate that the technology is now at a stage where an important agenda for positive change in agriculture can be established. This change could greatly aid in the economic development of the farming community.

In Ohio or Washington, the key issue for the next decade or more is, and will be, economic development. Our state and the nation as a whole are in the midst of an economic conflict. Recently, the senior vice-president of the Ford Motor Company spoke at Ohio University. He said: "We are in an economic war with other countries around the world and our whole way of life depends upon being one of the winners of this war. Industry and the private sector look to the minds within America's universities as allies for much needed help. If you will not commit your enormous talent to our struggle, we will look elsewhere and an irrevocable separation between two of the most important parts of our society will definitely take place." Economic development is one of those favored terms of our time. It is a term, moreover, that those in agricultural research universities must take very seriously during the 1980s and beyond. Although the agricultural components of universities have always had extensive two-way communication and interaction with the private agriculture sector through their extension services, this input usually has not been directed toward competitive economic development. Rather we have been either working with slight modifications in the *status quo* or involved with specialized research, which, although of utmost importance in the long run, does not aid the near-term economic needs of farmers and ranchers. Agriculture has supported the universities for several generations and now, as agriculture is facing the burden of economic crisis, it needs the special focus and mission-oriented emphasis of these institutions as never before. I don't know if my view from Ohio and the Midwest is darker and more foreboding than the view from other regions, but the present plight of agriculture here can be summed up by the words of a popular song by Bruce Springsteen: "It's like riding a downbound train." Ideas, abilities, and energy will be needed to bring about the economic revitalization of agriculture. Biotechnology offers one good mechanism to place the agricultural producer back in the mainstream of profitable national and world enterprise.

Accomplishing the goal of agricultural revitalization through technological innovation and the resulting development of new *high tech,* non-food products will require new partnerships and new interactions within the universities and throughout every sector of our society. Not only must long-term collaboration be prompted between the very finest biologists and molecular scientists in the colleges of arts and sciences and agricultural scientists in the universities, but new partnerships must also be formed with business and industry. The latter should include not only the established national or multinational corporations, who may have little vested interest in a region served by the university, but also those still unstable entrepreneurial start-up companies that will play a major part in forging the economic new order. No longer can the university community afford to give away its ideas to anyone and everyone, because these ideas can be used to fuel the economy of another region or even another country. We must learn to direct our ideas and new production systems to the rightful heirs of this technology: those who provided us with the means to do our work. Biotechnology centers in all areas must serve their regions as those of us at the Edison Biotechnology Center serve our constituents in Ohio. We must also share fairly for the betterment and development of all. This sharing will require new forms of partnership between our institutions and regions. These partnerships should be based upon the unique needs and capabilities of each participant and upon a sense of equality between participants.

This call for biotechnological innovation, agricultural economic development, and the establishment of new partnerships comes at a time when the nation is demanding excellence in higher education. And what better time for this challenge! The current passion for excellence has become a central theme in discussions of education. The new excellence demanded in higher education from many quarters should be more than a duplication or emulation of pre-existing patterns. Academic excellence for both state and private regional colleges and universities during the 1980s and 1990s, especially in agricultural programs, is not to be as much like Harvard, Stanford or MIT as possible, but rather to serve as a partner with government and industry in increasing the educational and economic opportunities available to their special constituencies. This excellence is far more adequately understood as a measure of performance than a repetition of preset patterns. For us at the Edison Animal Biotechnology Center here in Ohio, how we perform in integrating the new biotechnology into agriculture, so that it results in real economic gain for the farmers of Ohio and the rest of this country, will be our measure of excellence and their measure of survival.