

**Institute for Alternative Futures**  
**Foresight Seminars on Health and Innovation**

**SUMMARY**

FORESIGHT SEMINAR ON  
THE FUTURE OF BIOTECHNOLOGY  
December 15, 1982

**ABSTRACT**

The results of biotechnology, such as human insulin, have been much in the news in recent months, yet these are only the beginning of the applications of biotechnology. The current applications are, by and large, more effective ways to produce existing proteins or other molecules already existing in nature's catalogue. In the years ahead engineering at the molecular level could create a host of molecular machines able to sense and manipulate fine structures, for example cell repair devices to cure diseases- It could also create many other machines including some with military significance. The developments after a certain breakthrough point may be as significant as steam engines were in the past, or as artificial intelligence would be for the future.

The evolution of this field raises policy questions that will need Congressional consideration. The U.S. position as a leader in biotechnology will be shaped by policies towards research, education and the military classification of biotechnology information. As we approach the breakthrough point of a technology that may change all of society, our success may depend on the early recognition of the implications of that technology.

**BACKGROUND**

The rapid development of biotechnology in recent decades has already raised some major policy questions. Further development of this field will confront policy makers with additional ethical and political issues- The December 15th seminar looked to some of the future applications of biotechnology and explored some of the major policy questions that may arise. The first speaker, Eric Drexler, S.M., Research Affiliate at MIT Space Systems Laboratory and a science writer, spoke of the "decisive technologies" that lie ahead on the path which research is taking. These technologies will profoundly affect society. The next speaker, Kevin Ulmer, Ph.D., Director of Exploratory Research for the Genex Corporation, related Drexler's path of development to the situation today. He examined some of the pitfalls and difficulties of research and described what needs to be learned before breakthroughs will occur. The final speaker was Gretchen Kolsrud, Ph.D., Manager of the Biological Applications Program of the Office of Technology Assessment. She discussed some of the policy issues that may face the United States as biotechnology rapidly develops.

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**ERIC DREXLER**

Drexler presented a far reaching image of the future of advanced molecular technology starting with an analogy to the electronics field. In electronics we had big vacuum tubes several decades ago; then came the transistor working on the scale of a thousandth of a meter. Today we build devices on the scale of a millionth of a meter. Advances continue, yet the limits of that technology are now coming into sight. Molecular technology, with a different approach, will shrink devices by another factor of about a thousandth to a billionth of a meter.

In medicine, surgeons have been able to work on small levels using fine instruments, but they still come nowhere near to the molecular level of one billionth of a meter. Drugs are medical tools able to operate on a molecular scale, but organic chemistry has limits in the ability to build complex drug molecules and drug molecules can perform only simple tasks. In contrast, Advanced molecular machinery could combine the complex abilities and control of surgery with the power of drugs to work at the level of cells and molecules.

There are molecular analogues to the mechanical components that engineers use to make today's machines. For example, on the cellular level, flagellar motors act as motors, sigma bonds act as bearings, myosin serves as an actuator and ribosomes assemble proteins, guided by RNA tapes much as machine tools are controlled by punched paper tapes. In time we will be able to design protein molecules that can self-assemble to form more complex structures, as comparable proteins do in the cell; then we will be able to build complex machines on a molecular scale. This path of development leads to the possibility of assembling atoms together in large numbers to form molecular structures to an engineer's specifications.

This will make possible --after related biological research--the construction of cell repair machines. These could go to a part of the body needing repair, sense what needs to be done, then proceed to modify cells. White cells can be regarded as a kind of molecular machine already in the body. In the future, repair machines could be guided by a small computer with a gigabyte of memory (one billion bytes) programmed to recognize and destroy cancer cells, herpes virus or atherosclerotic deposits. The memory could be placed in a volume one-tenth of a percent of the size of a human cell. This sort of ability might not be needed for any particular disease, yet it is possible and shows what can be developed; it is a "decisive technology," like penicillin or smallpox vaccine, but with more general abilities.

We may compare today's knowledge in this field with that of space flight in the 1940's; all the basic knowledge exists, but considerable engineering work remains. We know, further, that Japan is competing with us in this field. The Research Development Corporation of Japan has initiated a five year, multi-million dollar program to develop molecular technology. Because this technology has broad applications outside medicine, including military potential, the outcome of the race to develop advanced molecular technology may well determine the future position of the United States.

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**KEVIN ULMER**

Looking at the same time frame as Drexler, Ulmer agrees that the technology will develop to allow us to position atoms and molecules at our whim. The question is how and when will this develop. Thirty—nine years ago, Watson and Crick discovered the structure of the DNA double helix. This was academically interesting but it took another ten years to discover the genetic code and yet another ten years after that before the first recombinant DNA molecules were created. This led to an explosion of both commercial and academic research. Now there is already humulin, or human insulin, commercially produced from DNA technology. The other projects companies are now working on are interesting economically and scientifically, but relatively mundane; it is a shifting from cell to cell of proteins that already exist in nature.

We are on the threshold of the next step; this is the engineering of materials outside the range found in nature's catalogue. Although nature offers a tremendous number of materials from which to draw, as we can see from the millions and millions of organisms on the planet, these are still the hand-me-downs of evolution. They all involve a fairly narrow range of physiological conditions to perform some specified function within the cell. They have not been designed to make bulk chemicals, for example, but they might well be used to do that if the design can be changed to include properties not found in the Living cell. To do that we will have to rely on some engineering.

To engineer the function of cells we will have to be able to specify where atoms are placed in proteins. Computer language offers an analogy: the nucleotides of DNA are equivalent to a four letter alphabet which can be grouped to form a sixty four word language which codes for twenty amino acids. These are grouped into sentences called genes, which are the basic units of cells. These can be grouped in coordinately expressed units like a paragraph. These may then be combined into books which describe the physical characteristics of organisms. Bacteria would be a book containing thousands of sentences. The human cell would have some three billion letters or millions of sentences; i.e., it would contain many books. A person in a lab today can read maybe a thousand letters comfortably, so it will take a long time to read the millions of letters that characterize the books typical of higher organisms. Writing, however, lags far behind and to get up to writing a million letters will take a monumental effort. We can already xerox, using enzymes, and edit, using recombinant DNA techniques. But only a few of the most sophisticated labs are able to creatively write in this language.

The functions of proteins vary because of the arrangement of their atoms. We don't understand how this basic chemistry works. However, we are in a position to ask some interesting questions and to take some tentative steps towards engineering. We start with an existing structure and an enzyme we already know. Then we make slight alterations in the hope of discovering new properties. These attempts have already been made and we are on the road to protein engineering. We can now view protein somewhat the way we do polyethylene, stainless steel and silicon; it is a material we can shape and build with. What we will build with new protein structures is not yet clear, but it is intuitively

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apparent that the possibilities are far broader than merely vaccines, insulins and industrial chemicals. We are talking about a world where we are controlling the precise arrangement of atoms to a high degree of specificity and where we take advantage of preexisting molecular machinery to do our work. We simply make a polymer and let the molecular machines, the bacteria, construct what we plan.

It is not clear what this will be good for or how long it will take, but the first steps have been made and the real applications of bioengineering lie along this path.

#### **GRETCHEN KOLSRUD**

Kolsrud began by asking three questions:

1. Are some of our customs and beliefs, and hence the political judgements in the form of laws and regulations which are the embodiment of those customs and beliefs, outmoded?
2. Are new processes needed to come to grips with some of the social, ethical and moral issues which will face us in the years ahead and what forms might those new processes take?
3. How pressing are these concerns?

Turning to the last question first, she noted that the rate of expansion of knowledge is particularly rapid in the field of genetics. For example, human insulin reached the marketplace in half the time anticipated when the work began four years ago. Human gene therapy is developing faster than expected, as indicated by Martin Cline's attempt to correct thalassemia in a severely affected young woman. Capability for successful single gene replacement therapy is not far off.

The fact that we may soon also have the capability to alter not only our own heritage, but that of our descendants as well raises major questions which will concern the policy maker. Examples of these questions are: 'What rights and responsibilities do we have to both those living today and those who follow? Now do we define a normal human being? What, if anything, should we alter? Is it all right to correct genetic diseases but not to permit sex selection? Now should we respond to the potential for directed positive eugenics of the human race?

The first broad policy issue concerns whether our customary casting of government and business in an adversarial relationship is outmoded. Our technological lead in the marketplace is declining as competitors use our own technology to win first place in world markets. We have a legacy of antitrust laws from a previous era when big business was seen to have adverse social consequences. It may be important to find mechanisms through which major corporations can develop and share knowledge in ways which are presently prohibited by our antitrust laws.

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The U.S. is embedded in a competitive world economy where the governments of other countries are actively promoting new technologies. Japan, for example, has designated biotechnology as one of its three "next generation technologies." MITI, a government ministry concerned with commercial development, has chosen three specific areas in biotechnology for concentration: bioreactors, mass cell culture and recombinant DNA applications. Fourteen major companies are working with MITI on these projects and have been organized into three "national research associations." Such associations are exempt from Japan's strict antitrust laws, and they can write off all R&D investments as tax losses. The breadth of interest of the Japanese government in biotechnology is shown by the fact that six other ministries besides MITI are also funding biotechnology projects. Japan intends to use biotechnology to remain dominant in certain world markets and they may succeed as a result of a policy of government and industry cooperation.

Another policy concern is whether new processes are needed to cope with the dilemmas new technologies will pose in the coming years, and if so, what these processes might be. Advances in communications technology are heralded by some as offering the potential for a more participatory democracy and a broader decision-making capacity. But this demands an informed populace when statistics suggest instead, a decline in scientific literacy in our nation. Fewer science and engineering degrees are being granted in the U.S. and, of those that are, more are going to foreign nationals. In 1980, foreign nationals received 46% of the doctorates in engineering granted in the U.S. Foreign nationals also receive a large share of the doctorates in mathematics and computer science. All of these fields are important to success in the race to commercialization of biotechnology.

These, and other problems posed to the U.S. by technological advances worldwide, can be solved. The question is whether it is the national will to solve them.

### **QUESTION & DISCUSSION**

Ulmer was asked if he was inhibited in his work by restrictive governmental policies and a lack of facilities. He said that he has seen two sides of the coin as most of the contract R&D his company does is for the Japanese. This is because the Japanese guidelines controlling recombinant DNA activity lags behind U.S. guidelines. Japan is still using P3 laboratories for work done in benchtop labs in the U.S. since NIH guidelines have been relaxed. The other side of that coin, however, is that the volume of money that Japan has put into the field already has them dominant on the engineering side of the business. Although they are behind us in the genetic technologies of molecular biology they can afford to play catch-up. Their stricter guidelines are only due to a time lag and the U.S. advantage will soon disappear. There is nothing to prevent the Japanese from catching up in molecular technology and with their engineering capacity they will be the dominant leader in manufacturing biological products.

When asked how far along the Russians were in biotechnology, Kolsrud said it is always difficult to be confident of the information from Russia, but they don't appear to be far

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along. Their major interest is in single cell protein. They have shortages in the enzymes and technological equipment needed for R&D in biotechnology.

A participant asked if comparing societies like the U.S. and Japan wasn't an ecological fallacy, whereby basic differences make comparisons meaningless like comparing apples to oranges). Kolsrud said countries face very similar problems differently and we may be at a disadvantage because of the approach we take. She acknowledged that deep cultural reasons may underlie our approach and change will be difficult. However, a global view may make some ideas, like government-industry cooperation, more desirable. Another participant noted that if we were like Japan. we would have big companies like Monsanto and Eli Lilly directed to do biotechnological research and there would not be small companies like Genex.

Kolsrud was asked if we need to redefine planning because of the speed of technological change. She answered that failure to look at the long term is presently characteristic of the U.S. system. We fear central planning, but it may be necessary to provide more coordination and coherent direction if we are going to compete against cultures that can direct their resources at problems efficiently. For example, today we aren't falling down on basic research but on production and marketing. If we look long—term we can see we will fall behind in research, too, if the trend of decreasing science and engineering education continues. We need a coordinated policy to correct this problem. We need not be like Japan, but we do need to set goals and achieve consensus about achieving them.

Drexler was asked about biotechnology as a mechanism for national advancement, particularly as a military critical technology. He was asked to comment on how this would effect the academic enterprise in this area. He said the technology is so broad in application that there are many potential military applications. Carbon atoms might be patterned to make materials with fifty times the strength to weight ratio of today's materials. This has obvious application in making aircraft. Superconductors could also develop from this technology and they would also have military uses. The policy issues affecting how basic research is done in this country are very difficult and despite a great deal of thought, Drexler sees no simple answers. Ulmer added that if biotechnology had been considered militarily significant and information had been classified, we probably would not have had the rapid development we've seen in biotechnology. Drexler agreed, but suggested that this may be an area where we have to accept a certain amount of cognitive dissonance, where we must pursue conflicting strategies at the same time. As an example of this he cited our policy of continuing to develop nuclear weapons while we try to negotiate a reduction of these same weapons. In the research area we need both competition and basic agreement and cooperation; this will become essential as the technology approaches the breakthrough point, and thus military applications.

Ulmer was asked if the lack of clarity regarding patents is a deterrent to sharing basic information and if this will inhibit research in the long-run. He answered that the patent situation is a mess. To protect themselves, companies try to patent everything and this is a financial drain that takes resources away from research. Part of the problem is that the

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patent office has not understood the state of the art. Hopefully, as the patent office becomes more familiar with the nature of research in biotechnology, patents will serve research rather than hamper it. Drexler added that patents are sanctioned monopolies allowed because they provide social benefits. They are awarded to reward and stimulate research and development efforts. The seventeen year patent, however, may be less appropriate as an incentive in a field that develops as rapidly as biotechnology. Many techniques and processes that are developed are important for a few years and then are surpassed. Often processes become the basis for further development and it could deter advancement if they are not readily or economically available for seventeen years. It may be appropriate therefore to issue shorter patents for certain types of discoveries, but to issue them more freely. It was also suggested that tax incentives might be more appropriate than patents to promote research, but Ulmer argued that this could give an advantage to the larger companies and not to small research organizations with little or no profits to tax.

A related question was whether international organizations were involved in biotechnology and patent issues. Kolsrud said there were, including OECD and UNIDO. Also, she noted that the World Health Organization passed a resolution on patents which could be harmful to research development if it were binding because it would give patent ownership for any projects involving WHO funds to WHO, thus discouraging additional private investment in biotechnology R&D. It was noted that at the International Patents Conference in Paris there was no resolution of differences in patent regulations.

A final question was asked about who pays for the basic research done in biotechnology in this country. Kolsrud responded saying venture capital is a major source for the early small firms. In 1980 and 1981 there were two firsts in public offerings on Wall Street. In 1980, Genentech went from thirty-five to eighty-nine dollars a share in the first twenty minutes. In 1981, Cetus obtained the largest amount ever obtained by that date in an initial public offering, \$107 million. This year has not been as successful in public offerings in biotechnology. However, larger firms are also investing in biotechnology. Dupont spent \$120 million of a total R&D budget of \$570 million on biotechnology. government has also put a lot of money in this area; in 1980, NIH earmarked over \$90 million for recombinant DNA projects. It is difficult to say exactly which research projects are defined as biotechnology, so there is no exact figure to give on government spending in the area.

### **CLOSING STATEMENTS**

Kevin Ulmer

The technology of manipulating molecules is inevitable, hopefully with significant applications within our lifetime. The concern is not if it will develop but how we should deal with it.

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Gretchen Kolsrud

The idea of different patent lengths is provocative and it may be worthwhile to explore policy changes in the area of the new technologies.

Eric Drexler

A long path of development in biotechnology lies before us, and the focus in this discussion has been on how to run fast. At some point on that path we will reach a breakthrough point, after which biotechnology will produce world changes more dramatic than those produced by the discovery of nuclear fission. We need early warning mechanisms to consider how society may change on the other side of that breakthrough point, and how we may prepare.