Chapter 3

Biotechnology and Unnatural Selection: The Social Control of Genes

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In his book, *The Second Genesis,* Rosenfeld (1975:32) introduced the term biosocioprolepsis or BSP. Building on the term prolepsis meaning anticipation, the word signifies the anticipation of biology's impact on society. The goal for BSP, according to Rosenfeld, is achieved "by projecting our imaginations ahead into our possible choice of social futures, we try to anticipate the dangers inherent in biomedical advance, and to forestall them by our foresight."

The social control of technological change has not progressed in this fashion. With very few exceptions, the pathological effects of technology have been controlled subsequent to their appearance in the industrial and domestic sectors when significant damage has already been done. Rarely are we faced with an opportunity of establishing safeguards for a technological revolution during its embryonic stages before it has become calcified into our economic system. That opportunity presents itself to us as molecular genetics is brought from the scientific laboratory to industry. But having a new term like BSP, a heightened consciousness about technology's dual edge, or critics who can conjure up prophesies of microbial chaos and humans fouling up evolution is not sufficient to

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provide the social guidance needed to intercede in what has been termed technology's autonomous path (Winner, 1977). We need institutional mechanisms to monitor, measure and test hypotheses related to the impacts of biotechnology on culture and ecology. The progress toward which we strive in exploiting nature's genetic secrets must have a counterpart in the progress we exhibit for developing social instruments of assessment.

For ten years, concerns raised about the revolution in molecular genetics have focused mainly on the problems of potential biohazards arising from laboratory experiments. The response to a cornucopia of conjectured risks of gene splicing has not been trivial. New relationships have been created between science and the broader society which supports its activities. These relationships are not only unique to the field of biology, but they are unprecedented for the entire enterprise of science. The changes that have taken place include: establishment of a federal office to issue guidelines and oversee the risk assessment for gene-splicing experiments; creation of local Institutional Biosafety Committees with community representation; enactment of laws by nine local governments and two states that regulate the use of recombinant DNA (rDNA) technology for research and commercial institutions (Krimsky, 1982; Dutton and Hochheimer, 1982).

The most noteworthy reform established during the decade made biologists who were engaged in rDNA research accountable to other individuals or institutions for the safety practices in their laboratories. Despite fears by some biologists, the involvement of non-scientists in the rDNA episode has not impeded scientific inquiry in any significant way (Singer, 1979; Setlow, 1979). New institutional mechanisms were developed to respond to a crisis in science over the safety of research. However we may interpret their effectiveness, the institutional forms reflect a greater responsibility of science and government to society. A system of social guidance, steered by scientists, but open to public involvement, undertook the difficult task of trying to assess the laboratory hazards of new technology. It was a rare opportunity for scientists to test their powers of BSP. But the preponderance of attention given to laboratory safety has masked other vitally important societal concerns pertaining to the commercial and military applications of genetic technology. My purpose in this chapter is to draw attention to the potential impacts of biotechnology that take us beyond the inadvertent creation of hazardous chimeric organisms.

The issues I shall raise about genetic technology are more fundamental than a list of actual or hypothetical concerns about its social, economic or environmental impacts. I inquire whether social institutions are in place that can address actual or potential problems associated with new developments in genetic technology, and whether our current institutions are appropriate to meet the demands of the problem. To the reader unfamiliar with biotechnology and rDNA molecule technology in particular, the following sections are offered as a primer to the field.

Rudiments of Biotechnology

The term biotechnology in its broadest sense means the application of biological processes for human purpose. The use of microorganisms to make beer and bread has been traced to antiquity (Demain and Solomon, 1981). In the 1940s the pharmaceutical industry began using microorganisms to produce antibiotics. However, in the last decade a substantial leap has been made in the commercial applications of simple life forms. This revolution is characterized by the expression genetic technology. All life forms from the simplest organisms such as bacteria and yeasts to higher mammals are made up of cells as the basic biological unit. Each cell consists of a set of instructions contained in discrete packets called genes. The genes are composed of threadlike molecules called DNA (deoxyribonucleic acid) grouped together in units called chromosomes. Bacteria consist of 2-3,000 genes on a single chromosome. Human cells contain 46 chromosomes with over 100,000 genes. The genetic instructions in the cell determine its growth and structure including its primary products—proteins.

Genetic technology refers to those processes through which the genetic instructions of a cell in the animal, in the test tube or in culture, can be controlled, manipulated, or transferred to other cells. For several decades scientists have been able to produce genetic changes in cells by the use of radiation, infection by viruses, chemicals, and exposure to pure DNA. Once the genetic changes were made, cells could be selected out for a particular purpose, such as hardier strains of wheat, or fungi that produce greater yields of antibiotics. In 1973 scientists discovered a method of wide applicability for transporting individual genes from one cell to another of virtually any species. This technique of recombining genes (recombinant DNA) meant it was possible to reprogram microorganisms to synthesize proteins that were completely foreign to them.

A typical recombinant DNA experiment involves three basic steps: (1) extracting a gene segment from a donor cell; (2) joining the gene in a test tube with a carrier DNA molecule (the foreign gene attached to the carrier DNA molecule is called the recombinant DNA molecule); (3) transporting the recombinant DNA molecule into the host cell.

The power of this technique compared to previous forms of genetic engineering is that it established genes as completely fungible elements capable of being transported between organisms however distantly related. Furthermore, it is a great advance over hit and miss methods of genetic engineering by mutation and selection.

When foreign genes are carried into bacteria the progeny cells of the microorganisms will get copies of the new gene. Under such conditions the foreign gene is said to be cloned or duplicated by the genetic apparatus of the cell. In addition to being able to produce large amounts of pure DNA through gene splicing, it also can be used to synthesize the protein encoded by the foreign DNA. Thus, by introducing the appropriate genes into bacteria these organisms can be

transformed into biochemical factories for synthesizing substances useful to medicine, industry and agriculture.

Medical and Industrial Applications of Genetics

In its widely circulated study, *Impacts of Applied Genetics,* the Congressional Office of Technology Assessment (OTA, 1981) cited five areas where rDNA will have the greatest impact: pharmaceuticals, chemicals, food, agriculture and energy. The respected financial weekly Barrons (Nossiter, 1982:8) reported that more than 100 specialized companies are trying to capitalize on the applications of gene splicing to these fields responding to markets estimated to pass $3 billion by 1990 (Patterson, 1981:66).

The earliest and most widely publicized application of recombinant DNA techniques is in the production of medically important proteins for use in research and the treatment of disease. Among the products currently being manufactured or still in the development stage are human insulin, animal and human growth hormone, clotting factors, antibodies, vaccines and interferon. From a scientific standpoint, virtually any human protein is subject to bacterial biosynthesis if the genes which encode it can be implanted and made to function in the bacterial environment. In vaccine production, the use of gene transplantation has made it possible to manufacture large quantities of non-virulent, nonselfreplicable segments of a virus that can be used to immunize a host. Two European companies are purported to be the first in the world to market a product manufactured by genetically engineered bacteria. Burroughs Wellcome of London and Intervet International (a subsidiary of the Dutch chemical firm Akzo A.V.) are manufacturing a vaccine to protect piglets and calves from scours disease (infectious diarrhea).

In agriculture, large investments have been made in rDNA molecule technology with the hope of producing a new class of "superseeds" even hardier and more fertile than those associated with the first "green revolution." Molecular genetics promises to provide the knowledge base underlying the genetic determinants of high yield strains. Among the most hotly pursued aspirations of rDNA technology applied to agriculture is in the area of nitrogen fixation. Certain bacteria and blue-green algae can transform free nitrogen from the atmosphere into ammonia which plants need for their growth. The bacteria which perform this function live at the root nodules of legumes such as soybeans and peanuts. But there are many valuable crops such as wheat, corn, and cereal grains, for which bacterial nitrogen fixation does not occur. For these plants, yields have been improved through the use of chemical fertilizers which have introduced many environmental problems.

The nitrogen fixation process is associated with a discrete set of genes (nif genes) in the bacteria. The new-found ability to move genes between species has

prompted three basic research strategies for improving on nature's use of nitrogen fixation: (1) increase the efficiency of nitrogen fixation for the plant-bacterial systems that currently possess this capacity; (2) genetically transplant the nif genes into new microorganisms; (3) genetically transplant the nif genes directly to plant cells making them self-fertilizing.

The food industry also has a serious eye on genetic engineering. OTA (1981: 107) cites two ways that microbial activity is used in food processing: (1) inedible biomass is transformed by microorganisms into food for human consumption or animal feed; (2) organisms are used in food processing either by acting directly on food or by providing material that can be added (such as enzymes and vitamins).

The prospect of revolutionizing the sweetener technology by developing cheaper methods for manufacturing pure fructose has encouraged an $8 million investment in the Cetus Corporation by the Standard Oil Company of California. The U.S. fructose market is estimated to be $11 billion a year. One of the first food-processing products manufactured by rDNA technology is rennin, an enzyme that turns milk into cheese. Collaborative Research with investments from Dow Chemical Company genetically engineered a yeast to express the enzyme.

In the energy field, bacterial strains are being sought which can economically convert agricultural and forest biomass into liquid fuels. Patents have been granted for genetically engineered microorganisms that can detoxify hazardous wastes or degrade oil spills. Currently, bacteria play a minor role relative to chemicals in the multibillion dollar insecticide industry. Approximately a dozen biological agents have been registered in the U.S. as pesticides. Scientists are looking for ways to improve the potency of bacterial strains on their pest targets by increasing genetic determinants of the toxins that destroy insect pests. Meanwhile, OTA (1981:89) projects there will be a revitalization of biotechnology in the chemical industry. It is expected that bacterial fermentation of certain substances will be substituted for selected chemical conversion chains that are part of the overall manufacturing process.

Considered along with computers as having enormous growth potential in the next several decades, biotechnology has touched off a major investment revolution. Most leading chemical companies are currently involved in genetic engineering either in-house or through patent and marketing agreements with smaller firms and universities (Fox, 1981:17).

The following are some highlights of the investment activity that had taken place by 1981 in the field of biotechnology. The Schering-Plough Corp. owned 16% interest in the Swiss bioengineering firm, Biogen. American Cyanamid had 20% equity in Molecular Genetics, Inc. The National Distillers and Chemical Corporation owned 11% of Cetus Corporation. Koppers Company, Inc., owned 48% of Genex Corporation. Dow Chemical invested $5 million for 5% of the common stock of Collaborative Research. Standard Oil had a 17% investment in Cetus Corporation. E.I. duPont de Nemours & Company was operating its

own genetics research facility and paid Harvard University $6 million for the exclusive rights to produce and market products that were derived from the university's genetics discoveries over a period of five years. Eli Lilly was involved in joint ventures with Genentech and entered into a long term agreement with International Plant Research Institute of California on improving plant yields. Phillips Petroleum paid $10 million constituting 35% equity in the Salk Institute Biotechnology Corporation which used to be a wholly owned subsidiary of the Salk Institute in La Jolla, CA. Mallinckrodt, Inc., a chemical company in St. Louis, invested $3.88 million in Washington University for research in hybridoma technology.

The Massachusetts General Hospital (MGH) signed a contract with one of the world's largest drug and chemical firms, Hoechst A.G. of West Germany. Under the plan Hoechst will provide MGH with $50 million over a decade to launch a major research program in genetic engineering in return for patenting and marketing rights. The Whitehead Foundation provided a $5 million operating budget and an initial $20 million grant for the construction of an independently run Whitehead Institute for research in molecular biology with cooperative ties to M.I.T. In the event of Mr. Whitehead's death, the new institute will obtain an additional $100 million under the agreement.

This inventory is only meant to be indicative of the investment activity in 1981; it is neither comprehensive nor suggestive of future trends. But it does help us understand the economic forces that are driving the application of rDNA technology into the commercial sphere.

Against the current of the extraordinary investment fever, there are some who question how this technological wonderland of genetic chemistry will affect our society. A former chairperson of both the Recombinant DNA Advisory Committee (RAC) and the House Subcommittee on Science, Research and Technology, Ray Thornton (1981), made the following poignant remark to the RAC: "Human experience has shown that any tool powerful enough to produce good results of sufficient importance to shake Wall Street and offer hope of treating diabetes is also powerful enough, wrongly used, to produce bad results of equal consequence."

In the context of these remarks I shall address five areas of social concern for the field of biotechnology.

Harnessing rDNA Technology

Now that molecular biology has important social applications why doesn't our government establish priorities for harnessing gene-splicing technology in the interest of the greatest number of people? Is there any justice in allowing the free market to determine whether and to what extent gene splicing improves people's living conditions by determining what products are introduced into the market

place? Three arguments have been advanced in support of a strong governmental role in exploiting the social uses of genetic engineering.

Argument 1. Since public monies were the principal source of funding through which rDNA methods were developed, the public sector should play a major role in directing its use. A corollary to this position states that the public is entitled to a return on its investment and should control the patents on products and processes that grow out of federally funded research.

Argument 2. If social priorities are not set for the use of rDNA technology then the public will miss out on important applications which private markets will not find profitable to pursue. A case in point is "orphan drugs" which illustrates the need for governmental involvement in the development of pharmaceuticals. The drugs are so named because they cannot find a parent company who will invest in their manufacture. The markets for the drugs are too limited to provide a satisfactory return on investments. Few question, however, the responsibility of society to make available for clinical use non-profitable drugs if they are effective in aiding even a small number of patients.

Argument 3. When the fruits of rDNA technology are realized, such as in agriculture, it is the responsibility of government to guide the benefits so that they are at least shared equitably and at most shared in a manner that narrows distributional gaps. In the case of agricultural impacts, a guidance system can insure that small farmers are not disadvantaged from new strains of genetically engineered seed stocks, that the consumer gets a better quality product at a more reasonable price, and that environmental health is not traded off for higher rates of return.

For the purpose of this discussion I shall suspend judgment on the cogency of the arguments. They form an essential part of the background criticism that has been raised against the fledgling gene-splicing industry. Hundreds of biotechnology firms have surfaced in a highly competitive marketplace with their own sets of agendas and perceptions of social needs. Returning to my initial query: Are there institutions which can establish priorities for harnessing rDNA technology? What assurances are there that private and public investments in the field of biotechnology get channeled into uses that are responsive to distributional inequities.

Currently, no single institution has the authority to set and implement priorities for the application of gene-splicing methods to industrial, agricultural, or clinical areas. Moreover, there is little, if any, precedent in this country to guide the development of a technology of such broad scope. While we have governmental institutions for setting research agendas, assessing and controlling technological impacts, and overseeing targeted programs in applied technology, private markets are fundamentally responsible for what gets produced, in what order and toward what end.

In theory at least, the Office of Technology Assessment possesses an excellent vantage point from which to establish a set of priorities for developing

rDNA technology. But on the basis of its evolving role over the past several years, which excludes advocacy of particular policies and actions, it is highly unlikely that OTA would be the body to establish a hierarchy of needs from which to develop a strategy for extracting social benefits from the technology. Different agencies of government such as the Department of Energy (DOE), the Food and Drug Administration (FDA) and the Department of Agriculture (USDA) will set their own agendas. However, the public has little access to how these agencies establish their individual priorities.

Recently, the Plum Island Animal Disease Center (USDA) and the bioengineering firm Genentech, Inc., entered into a cooperative agreement to produce a vaccine for foot and mouth disease. For many countries outside the United States, the highly infectious foot and mouth virus is responsible for substantial losses in beef stock and milk production. Fortunately, North American agribusiness has been spared the disease for many decades because of strict beef import controls. It is argued that American consumers could benefit from a worldwide eradication of the disease. For Genentech, the carrot in this public-private partnership is the right to foreign markets for vaccine sales, a sizable benefit for a small firm that entered the vaccine research program in its final stages.

Broader public input for setting agency priorities could come from Congress through its appropriate subcommittees on science and technology. In its report *Impacts of Applied Genetics,* OTA (1981:10–12) generated several options for Congress to consider with regard to promoting advances in biotechnology. The options included: establishing a funding agency in biotechnology; creating federally financed research centers in universities; providing tax incentives to expand the capital supply to small high risk firms; improving conditions under which U.S. companies collaborate with academic scientists; mandating support for specific research programs. Each of these recommendations has been used in the past to stimulate or set a direction for the development of innovative technologies. But the approach taken by OTA does not address the question of setting overall priorities for the utilization of rDNA technology on the basis of social needs. Precedents in this country run against this type of endeavor which might be termed national technology planning.

In contrast, the federal government has taken an active role in shaping the direction and quality of research, both targeted and basic, through funding mechanisms (Cooper and Fullarton, 1978). It is estimated that about two thirds of all the basic research carried on in the U.S. is federally supported. But the public sector role has been minimal to almost nonexistent in directing the application of technologies. It is widely assumed that social needs will be more effectively revealed through market forces. With due respect to the sudden growth of economic fundamentalism, there are many areas where the assumption fails miserably. A former member of the White House Office of Science and Technology Policy and an astute observer of genetic technology offered this prognosis (Omenn, 1981:44).

> There is certain to be a shake-out in biotechnology over the next five years or so, and the determinants of success are likely to be related more to business strategies, shrewd management, and high quality control, assuming a strong base of laboratory talent. Chemical and agricultural products will be marketed in short order, if they are economically competitive, but hormones, drugs, and vaccines must undergo complex and expensive clinical trials. There can be little doubt that the Wall Street criteria will be applied: earnings, growth, profitability.

Since gene splicing is expected to introduce innovations in several commercial fields, if a hierarchy of needs is conceded to be desirable, it seems more reasonable that it be achieved within specific areas, such as vaccine production, chemical processing, biomass conversion and agricultural products. Federal agencies such as FDA, DOE and USDA could set priorities in biotechnology with appropriate inputs from the public. It has also been suggested that "we might set as a national goal the conversion of an economy based on fossil fuel to an economy based on microbial fermentation" (Lewis, 1981:46). A national effort, on the scale of the space program, that promotes the development of inexpensive, renewable energy sources from biotechnology would improve significantly the public's confidence in science and technology.

In the pharmaceutical field, who decides what gets manufactured first, bovine growth hormone to fatten up cattle or human growth hormone as a replacement therapy for a genetic defect? Should a vaccine for malaria get precedence over one for Herpes virus? Other factors besides profit and social demand will invariably enter into such determinations, such as how far advanced the state of knowledge is toward a solution of a particular genetic engineering problem. Considerations also include what sources of private and public capital are available for specific product development. Products with low market potential are likely to be left behind. There are no established institutions or advocacy networks through which the public sector can make its voice heard on priorities in technological innovation. Yet the public has been promised so much from biotechnology in such a short time that federal responsibility and initiative in supporting a development program deserves careful consideration. The first step is to recognize the legitimacy of the citizenry in steering a technology. The next step is to develop avenues of participation and social guidance mechanisms.

Technology Transfer to the Third World

Among the important applications of biotechnology, some will eventually be exported to third world countries. What responsibility do we bear in the transfer of this technology to the developing nations? On one hand, the industrialized world must find ways to share the positive fruits of genetic engineering with developing nations without destroying their unique cultural forms, neglecting

their capacities for self-determination, or disregarding the needs of their economic systems. On the other hand, we bear an obligation to prevent the export and development of products and processes that we determine to be unfit for ourselves or which would be unsuitable for the cultural patterns and technological development of the country in questions.

Very soon after plasmid-mediated transfer of chimeric genes was discovered, its commercial applications were being seriously investigated. One scientist, who was employed by a major U.S. corporation, saw in genetic engineering a solution to the problem of world hunger. This scientist was planning to construct a plasmid with genes from *Pseudomonas* that code for enzymes with cellulose-degrading properties. He considered cloning the plasmid with the cellulose-degrading genes in *E. coli*. His logic for using this organism to alleviate world hunger was as follows: suppose that vast populations in underdeveloped food-scarce countries could have their intestinal flora transformed or replaced with the new cellulose-degrading *E. coli*. With their new intestinal flora, these individuals could presumably obtain caloric value from vegetation that is plentiful and inexpensive, but under the present circumstances nutritionally useless to them. After being advised by a scientific colleague that cellulose-degrading *E. coli* in the gut could eliminate any roughage in the digestive tract and thus increase the rates of certain disease correlated with low fiber diets (obesity and bowel cancer were cited) the investigator gave up his plan (Krimsky, 1982:117-119).

I offer this story not to emphasize the potential hazards of such a scheme nor to question the motives of responsible scientists, but to remind us that the idea was being considered for use exclusively in the poorer nations of the world. Currently, transnational corporations market and export products to developing countries which are either prohibited or severely restricted for domestic use. Recent publications and television documentaries have illustrated these problems for the export of pesticides and pharmaceuticals (Schulberg, 1979; Weir and Shapiro, 1981; PBS, 1981). There are no U.S. federal agencies with authority to prohibit the export of domestically banned products even when they are manufactured in this country. Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and Toxic Substances Control Act (TSCA) there is a statutory obligation to inform foreign governments of regulatory actions taken against specific products. Also, under TSCA, companies are required to make toxicity information on chemical products available to foreign import countries. Notwithstanding the legality of the transactions, and those cases of domestically-banned exports whose benefits to the import country clearly outweigh their adverse effects, there remain many areas where the ethical practices of the exporting firms are of a questionable nature.

Just prior to leaving office President Carter signed an executive order (15 January 1981) that placed export controls on extremely hazardous substances deemed a substantial threat to human health, safety, or the environment. Once classified, these products would require an export license. Carter's order took two

years to develop. It was in effect for only a month when it was revoked by President Reagan (Shaikh and Reich, 1981).

Within a couple of years the first commercial products of rDNA technology will be reaching consumers. It is reasonable to expect the problem of questionable exports to be compounded as biotechnology's pioneers seek world markets. For example, since pesticides contaminated with dioxins are already being sold to some developing countries, there is also a market for the biological antidote—organisms genetically engineered to degrade this class of pesticides. The media have recently reported the development of a new genetically engineered bacterium which degrades the herbicide 2,4,5-T. Its creator, who also developed an oil-eating bacterium, was quoted as saying: "If you use 2,4,5-T to kill weeds one year and then apply these microorganisms to clean up the 2,4,5-T . . . their number will die out drastically when there is no more of the chemical to eat" (Chakrabarty, 1981). Under such ideal but unrealistic conditions, the microbes will not mutate, establish themselves in new niches, nor adversely affect the microflora of the land areas on which they are sprayed. Less dubious assumptions have been responsible for creating havoc in sensitive ecological systems.

Our current experience with exports of hazardous materials and the transfer of certain inappropriate technologies to industrially underdeveloped agrarian societies leads me to the conclusion that unless more responsible institutions are created, similar mistakes will be made when the fruits of rDNA technology become realized. The widely used justification that importing countries are free and willing to buy products of dubious value fails the test of moral reciprocity. The Carter executive order was a positive step toward a global responsibility for our exported products. With that order rescinded, an additional burden is placed on scientists and the public health community who are familiar with the deleterious effects of chemical or biological exports to inform the recipient countries and the World Health Organization before rather than after severe injury or environmental damage is incurred.

Secondary Impacts

The products, processes, and industries that eventually emerge as a consequence of the commercial applications of molecular biology will undoubtedly exhibit unintended secondary impacts. For example, if a vast array of new or old pharmaceutical products are manufactured at low cost (including antibiotics and insulin), what effect, if any, will that have on drug overuse? Harvard biologist Ruth Hubbard (1977:165-169) assessed the use of rDNA technology for the production of insulin at a meeting of the National Academy of Sciences: "given the history of drug therapy in relation to other disease, we know that if we produce more insulin, more insulin will be used, whether diabetics need it or not."

If agricultural plants are engineered to be resistent to herbicides, will that

stimulate a greater use and dependency of chemicals in agriculture? If microbes are developed which can degrade herbicides containing dioxins, will that justify the removal of restrictions on this class of potent chemicals when they are used in conjunction with their biological antidote?

It is easy to raise hypothetical cases. I do not pretend to have any skills as a technological forecaster. I use these not-so-implausible cases to reintroduce the theme of my inquiry: Are there social guidance systems through which society can anticipate, or at least keep track of the secondary consequences of major technological innovations?

In the late 1960s, the term technology assessment became a part of our policy vocabulary. The National Environmental Policy Act established a requirement for environmental impact assessments for many government supported projects. Even the NIH guidelines for recombinant DNA research were issued with an environmental impact statement (USDHEW-NIH, 1977). Some laws and institutions are already in place to respond to the potential impacts of biotechnology. None, however, are equipped to provide continuous monitoring and assessments of the full range of expected commercial uses of gene splicing, and other tools of biotechnology such as cell fusion, over a period of years.

In principle, the Office of Technology Assessment is well suited to carry out this function because it has been able to assemble highly trained interdisciplinary teams of scientific and policy experts. But as an agency of Congress, OTA will undertake studies when there is sufficient congressional support. In its recent report on applied genetics, OTA chose to place considerable weight on the positive social outcome of genetic engineering including increased manpower needs, new products, and improved yields in agriculture. But only a feeble effort was made in this study to evaluate potential adverse social or ecological consequences of industrial microbiology. No research program or framework for long-term assessment is offered.

A second study by OTA started in the fall 1981 evaluates the competitive position of the United States in the global biotechnology field. In the scope of project activities there is a striking absence of any reference to the assessment of secondary impacts. For OTA, technology assessment in the field of biotechnology has come to mean promotion, pure and simple.

Individual agencies also bear responsibilities under legislative mandate to evaluate products of rDNA technology. But evaluations of this nature are spotty and restricted in scope. The FDA is primarily concerned about the efficacy, purity, and the side effects of a new drug, but cannot rule on its broader social manifestations. The Environmental Protection Agency (EPA) has no authority to restrict the use of pesticides on the grounds that they might exacerbate the decline of small farms. (See the chapters by Dorner and Thiesenhusen for the effects of technology on small farms.) Under a variety of statutes EPA does have authority over the release of hazardous materials into the environment. However, no regulations currently exist or are anticipated that restrict the release of

biological agents into the environment with the sole exception of biological pesticides which must be evaluated for safety and efficacy according to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) before they are registered. While initially planning to issue regulations for infectious wastes under the Resource Conservation Recovery Act, EPA has changed its approach under the Reagan administration. Its current effort is directed at publishing an infectious waste management plan to help industry on a purely voluntary basis become acquainted with accepted practices for disposing of biological wastes.

It is clear that biotechnology is today where the petrochemical and nuclear technologies were forty years ago. Our experience in these fields should not be neglected. Without adequate guidance systems the social consequences of technology come without advance warning and in a form in which effects are all too often irreversible.

rDNA and Biological Weapons

The feasibility of creating biological weapons with rDNA technology was on the minds of those who attended the Asilomar conference in 1975 where scientists from 15 nations met to discuss the science and potential risks of gene splicing. Despite expressed concerns by some participants, the issue was kept off the agenda by the conference organizers for fear it would interfere with the primary goal of reaching a consensus on laboratory biohazards (Krimsky, 1982:106). Nevertheless, one of the three working panels at Asilomar concluded its report on the assessment of risks with the following admonition (Plasmid Working Group, 1975:19):

> We believe that perhaps the greatest potential for biohazards involving genetic alteration of microorganisms relates to possible military applications. We believe strongly that construction of genetically altered microorganisms for any military purposes should be expressly prohibited by International treaty. . .

Just a few months prior to Asilomar, the United States Senate ratified the articles of the 1972 Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological and Toxin Weapons. The Convention's articles were put into force in this country by March 1975. Nearly a hundred countries had already pledged "never in any circumstance to develop, produce, stockpile or otherwise acquire or retain (1) microbial or other biological agents . . . whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; (2) weapons, equipment or other means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict" (Bacteriological and Toxin Weapons, 1975:5).

According to Article XII of the Convention, a review is to take place five years after it has been in force to examine the relevance of new scientific and technological developments. A United Nations review committee report issued on March 1980 concluded that biological materials constructed by rDNA techniques were unambiguously covered in the Convention's language (Preparatory Committee, 1980:7). The committee also assessed the potential use of rDNA for creating biological weapons. The prospect of developing fundamentally new agents or toxins with rDNA technology was viewed as a problem of "insurmountable complexity." The committee saw little incentive for such efforts since "naturally-occurring, disease-producing micro-organisms and toxins already span an exceedingly broad range, from some which are extraordinarily deadly to others usually producing only temporary illness." However, the committee considered more probable the use of rDNA techniques to improve the effectiveness of existing biological warfare (BW) agents.

What assurances does the public have that present or future administrations will adhere to the articles of the Convention? What institutions are currently available to provide the public with information on biological research programs carried out within or funded by the Department of Defense? Is there a clear distinction between offensive and defensive biological weapons? Does it even make sense to speak about defensive biological weapons? What would they be and is their production restricted by the Convention?

As an example, might the army want to clone toxigenic genes into wild type *E. coli* to assess the potential use of gene splicing by a hostile state or terrorist group? Should our defense establishment be funding projects to make vaccines for pathogens that do not currently exist? According to a 1980 report, DOD has expressed an interest in assessing whether genetic engineering can be used to make new biological weapons (DOD, 1980, sec. 2:4).

> New threats may be opened up by various technological and scientific advances. As examples, recombinant DNA technology could make it possible for a potential enemy to implant virulence factors or toxin-producing genetic information into common, easily transmitted bacteria such as *E. coli.* Within this context, the objective of this work is to provide an essential base of scientific information to counteract these possibilities and to provide a better understanding of the disease mechanisms of bacterial and rickettsial organisms that pose a potential BW threat, with or without genetic manipulation.

To improve its understanding of these possibilities the U.S. Army has begun some rDNA work. Its medical Research Institute of Infectious Disease received permission from the RAC to clone *Pseudomonas* exotoxin in *E. coli (Science,* 1980a). The Army Medical Research and Development Command advertised in *Science* for proposals on the introduction by rDNA methods of the human nervous-system-gene acetylcholinesterase into a bacterium *(Science,* 1980b).

The expressed purpose of the research is to develop an effective antidote for nerve agents manufactured by the Soviets which are extremely potent cholinesterase inhibitors. The Army's interest in cloning the enzyme is to obtain a sizable quantity of high purity material so that its physical and biochemical properties can be studied.

What windows of accountability exist between the military and the public on the uses of genetic engineering? How can public skepticism be turned into public confidence? Presently, there are three institutional responses that serve to build public confidence: the 1972 Convention previously mentioned; a federal law requiring the DOD to describe its obligated funds in chemical and biological research; and the NIH guidelines. The second institutional response gives Congress and the public more direct access to the chemical and biological research carried on by the military. According to Public Law 91-121 passed in 1969 and amended in 1975 (P.L. 93-608) the DOD is required to submit an annual report to Congress that explains each expenditure in its chemical warfare and biological research programs including those designed for "development, test and evaluation and procurement of all lethal and nonlethal chemical and biological agents."

The third instrument of social accountability is the NIH guidelines. A memorandum from the Undersecretary of Defense dated April 1, 1981 states that "all DNA activities funded by DOD, whether in-house or by contract or grant, will be conducted in full compliance" with the NIH guidelines (Wade, 1981). The ruling specifies the use of institutional biosafety committees and requires that a complete file of each research project be maintained for public scrutiny at the U.S. Army Medical Research Institute of Infectious Diseases.

It appears then, that if the Army wishes to clone toxigenic genes into wild type *E. coli,* current DOD policy requires that these experiments must first receive approval from the RAC and subsequently be registered. There is no reason to believe that DOD will not adhere to the principles of the Convention. At issue here are the bridges of confidence that must exist between the public and the military in the context of possible alternative interpretations to the language of the treaty.

For example it is not clear whether the Convention language prohibits the construction of new or improved pathogenic strains of bacteria if the putative interest in such agents is either to determine their strategic capability for military and civilian populations or to aid in the manufacture of a vaccine against them. On the conjecture that some nation has the capability to construct a new strain of a virulent organism that could serve as a BW weapon, another may decide to construct it first in order to develop a vaccine. Our defense establishment becomes particularly vulnerable to this type of thinking when fears are raised about the escalation of Soviet chemical and/or biological weapons activity (Marshall, 1981).

Richard Goldstein, a molecular geneticist at the Harvard Medical School and member of the RAC, argued that the DOD can construct altered forms of

virulent pathogens for biological warfare and still be conforming to the principles of the Convention "if the rationale is that the work is being done for prophylactic, protective and peaceful purposes." Under the Convention's rules Goldstein believes that a country can work with superpathogens, produce vaccines against such agents, and develop the dispersal systems for delivery in order to defend itself against a BW system. "[H]aving perfected such systems under the blessings of the Convention (i.e. for defensive purposes), DOD in reality has a cleverly disguised offensive capability for biological warfare" (Goldstein, 1982).

Some time in early 1982, a confidential proposal was sent by the Army to the National Academy of Sciences which described classified experiments it was prepared to fund. According to a report in the British science journal *Nature* (Budiansky, 1982:615) the experiments included "the possible offensive uses of recombinant DNA technology in biological warfare, ostensibly for the purpose of better understanding how to defend against them." The contents of the proposal leaked out and the military use of rDNA molecule technology became a subject at the June 1982 RAC meeting. Richard Goldstein and former RAC member Richard Novick of the Public Health Research Institute of New York City proposed the following amendment to the NIH guidelines:

> The use of recombinant DNA methodology for the purpose of development of microbial or other biological agents or toxins as biological or chemical weapons is prohibited as consistent with the spirit of the 1972 Biological and Toxin Weapons Convention.

The RAC defeated the proposal and instead passed a motion to remind the Director of NIH that the Convention prohibits the use of rDNA methods to produce agents not used for "prophylactic, protective or other peaceful purposes." Meanwhile, it has become clear that there will be no public oversight of the classified research funded by the DOD assessing the potential of rDNA for biological weapons which could involve the construction of pathogens totally unique to the ecosphere.

Human Genetic Engineering

The discovery of gene splicing as a tool of scientific inquiry received considerable media attention because of the initial concerns about producing hazardous organisms. But even as these issues were debated sectors of society began to draw attention to human genetic engineering. States and local communities that took up the regulatory issues were confounded by the ethical ones, if they considered them at all. The exception is Waltham, Massachusetts which passed a law that forbids the use of humans in rDNA experiments. The human-experiment provision, tagged on to its ordinance regulating rDNA activities, did not result from a

broad community debate, but was prompted by a single member of the city council.

What safeguards are in place to protect society from the potential misuse of biotechnology in human genetic engineering? Are there any ethical thresholds which should be considered when applying genetic engineering to the treatment of disease or in conjunction with other reproductive technologies? Should limits be set beyond which clinical research in human genetics becomes impermissible?

It is not difficult to conjure up insidious forms of human genetic manipulation as in cloning of an individual. Nor is it problematic to think of humane uses for genetic therapies. But there is a vast middle ground for the human applications of genetics for which a consensus does not exist among scientists, ethicists, members of the religious community and the general public. Some view alteration of germ line cells as morally reprehensible. Others argue that we bear just as much an obligation to eliminate from the gene pool the determinants of Tay Sachs and sickle-cell anemia as we have to eliminate smallpox from the planet. Germ line cell surgery may be the only way to achieve such a goal.

In 1977, at the National Academy of Sciences' Academy Forum devoted to genetic engineering, a scientist tried to put into perspective both the lofty claims and the exaggerated fears being expressed about rDNA technology. Questioning the promise of genetic surgery he said: "How about a thalassemic? Are we going to drain his marrow out, then culture his cells, get DNA in (the cells) and put (them) back in (the person)? Quite frankly I would rather be a thalassemic than have that happen to me" (NAS, 1977:170).

However incredulous the implantation of genetically engineered cells may have appeared at the time, just three years later a UCLA investigator performed a remarkably similar procedure in what has been deemed the first human genetic engineering experiments. These experiments were conducted in Israel and Italy using Italian and Israeli subjects, who voluntarily consented to participation. The subjects in question were suffering from a life-threatening blood disease (beta thalassemia major) in which the bone marrow cells are unable to produce normal hemoglobin because of defective genes.

The UCLA investigator removed bone marrow cells from the patient and exposed the cells to normal genes for making hemoglobin. The human genes were cloned by rDNA techniques. The genetically engineered bone marrow cells were reinjected into the patient in the hope that they would prosper and produce blood cells with normal hemoglobin. The individuals treated by this procedure were experiencing the final stages of the disease and given the prognosis of a limited life expectancy (Schmeck, 1981:20E).

Similar protocols were not approved for experimentation at UCLA by that institution's human experimentation committee. After holding the application for fourteen months, the UCLA Human Subjects Committee was unwilling to approve the experimental procedure on the grounds that there was insufficient evidence of its success in animal systems.

What can be said about the current institutions available to handle such questions? Committees for the protection of human subjects, whose operating procedures are defined in federal guidelines, issue independent judgments at each institution. But human genetic engineering represents a quantum leap in the use of humans as experimental subjects. There are more issues at stake than the protection of the rights of privacy and well being of individual subjects.

In cases where the genetic engineering is performed on the fertilized egg *in vitro* (combining genetic engineering with *in vitro* fertilization) review by human subject committees is not required. It is conceivable that the Recombinant DNA Advisory Committee could address the issue of human genetic manipulation. But its current charter and membership is designed to keep RAC's attention exclusively to biohazards and away from ethical problems.

There is another institutional process for reviewing human genetic engineering experiments in the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Since the Commission can only issue recommendations, it cannot provide the oversight to local human subject committees unless Congress acts or some initiatives are taken by the Department of Health and Human Services which oversees the human subjects regulations. Without some general guidelines establishing ethical norms for human genetic manipulation experiments, the responsibility for developing such policies will be relegated to individual institutional committees. And while the possibilities grow for human genetic therapies, e.g. gene splicing in conjunction with *in vitro* fertilization, and mammalian cloning, free floating public anxieties are in search for an institutional response.

Conclusion: Technology's Double Edge

The medical and commercial applications of gene splicing raise some old problems fashioned in new suits of clothing. The developments in a field bursting with innovative ideas and unlimited potential will put to the test the social guidance systems we presently have. But more so, they will test the moral and scientific wisdom of technologically advanced countries on their capacity to counteract the adverse effects of genetic technology before they are realized and become part of the social and economic infrastructure of society.

Scientific knowledge, said Bacon, is power, and power comes in two denominations, liability and assets. It is unthinkable that nature will release its genetic genie in only a single denomination. That type of technological accounting results in moral bankruptcy. The key to sound technological bookkeeping is in the development of guidance systems whose sole function is to trouble-shoot biotechnology's social impacts. Efforts toward this goal have been notable in the areas of laboratory safety and to a lesser degree, military applications. Initiatives in other areas have been nonexistent.

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