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MEDICINE, TECHNOLOGY, AND GENETIC ENGINEERING: REFLECTIONS FROM THE OUTSIDE

by

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Abstract

Advances in technology are producing many changes in the ways humans view and manage their lives. The refinement of genetic engineering techniques has created vast opportunities for humankind, along with novel problems and dangers. Accordingly, the questions that must be addressed pertain to the nature of life itself. Yet the scientific community can not be given sole discretion in managing today's technologies. Instead, all segments of society must be involved in determining how genetic engineering will be used.

Of all the areas of human endeavor, technology most often affects the field of medicine. The marriage of technology and medicine - science applied to the art of healing - influences persons in a manner unlike any other type of scientific undertaking. Changes in the "technology of medicine" come fast and furious, and usually involve questions concerning the nature of death and sickness. Moreover, these questions have more than academic significance to the public. Along with the benefits of medical technology are, of course, problems to be addressed.

A growing number of critics claim the marriage of medicine and technology is not necessarily a match made in heaven. They feel changes in technology are threatening society's moral foundation, destroying person's perceptions of the meaning of life, and endangering the existence of the human species.[1]

Ethical questions in the medical field are prevalent, but certainly not new. The answers to such querries can prove evasive and controversial. For example, the issue of abortion has sparked bitter discussions. On December 1, 1982 Mr. Barney Clark opened a new chapter of medical history, with the first human use of an artificial heart. As a result of

this development, questions about the quality and cost of life have intensified.[2] However, one particular technology, with extensive applications both within and outside the field of medicine, is giving rise to questions that go beyond those already raised. Visions from Aldous Huxley's Brave New World are becoming realities through the technology known as genetic engineering.

A Definitional Introduction

Genetic manipulation, genetic engineering, gene splicing, and gene therapy are terms that conjure up vivid and sometimes horrifying mental pictures. Genetics - the science of heredity - has been around for sometime, but recent scientific advances have dramatically altered its significance. To analyze the various societal issues involved with today's genetics, the basic scientific principles must be outlined and defined.

Many of the domestic animals, crops, and plants in existence today are human creations. They are the result of a selective breeding process aimed at enhancing desired characteristics. This fairly innocuous "genetic manipulation" has raised little outcry from the public. Of more recent origin is "genetic engineering", a term that denotes a more active intervention in the evolutionary process.[3]

All living organisms are composed of cells; the human body contains billions of cells. Most cells share a common structural design, including a nucleus that stores genetic information. Within the nucleus are pairs of chromosomes. Each chromosome contains a long thread of deoxyribonucleic acid, or DNA. DNA - the key to contemporary genetics - has been called the "master molecule of life", as almost all living organisms possess it (Judson, 1979). Portions of DNA contain coded instructions which enable a cell to perform a particular function, e.g., to manufacture a necessary protein. These DNA segments are called genes, and they are central to understanding heredity. It is through genes that the blueprint of life is passed from one organism to its offspring, from a mother and father to their child. And it is on these genes the spotlight of science and the heat of debate currently falls.

Genetic engineering refers to the genre of technology that utilizes a range of procedures that add genetically determined characteristics to cells that would not otherwise possess them, or would acquire these traits only after many years of development. Gene splicing, a form of genetic engineering, involves the technology of recombinant DNA. With this

technique, sections of DNA can be removed from one chromosome and fused with a chromosome of another cell. Thus DNA from different species can be combined to create a new organism. Gene therapy is the use of gene splicing to introduce a normal functioning gene into a cell that contains a mutant or defective gene.

The Business of Genetic Engineering

Advanced Genetic Sciences, Genex, Agrigenetics, Cetus Madison, and Genetech are not household names. Yet they are five of the largest corporations involved in the genetic engineering business. According to a recent Department of Commerce (1984) report, several hundred U.S. companies are now employing biotechnology (genetic engineering). Present estimates of the total market for their products by the year 2000 range from 15 to 100 billion dollars.

Wall Street has not ignored the glamor and appeal of the new technology companies. Genetech was formed in 1976 to utilize patented recombinant DNA technology. In 1980 its initial stock offering set a Wall Street record for the fastest rise in price per share, going from $35 to $89 in 20 minutes. The following year, Cetus Corporation set a Wall Street record for the largest amount of money raised in an initial offering, or $115 million.

The biotechnology industry was spawned largely through government expenditures. Over the last 30 years there has been growing federal support for basic biomedical research. This support has created the knowledge and personnel base that provides the foundation for current bio-technical activities. The leading federal agency involved in research has been the National Institute of Health (NIH). The NIH, consisting of 11 institutes and many programs, constitutes the world's largest biomedical research laboratory. Its present budget of over $3.3 billion supports the work of the Institute's 3000 scientists and 2000 laboratories. The NIH spends 80 percent of its budget to support outside research at hospitals, universities, and other laboratories.

The business of genetic engineering is not without regulation. Regulatory power over the biotechnology industry is possessed by at least 17 federal agencies.[4] Which agency has jurisdiction depends on the product manufactured or the research undertaken. For example, the Food and Drug Administration (FDA) approves human drugs, diagnostics, and food additives, while the Department of Agriculture has jurisdiction over research conducted on plants and animals. The NIH Recombinant DNA

Advisory Committee (RAC) has authority over basic research. Due to overlapping jurisdiction, turf disputes between regulatory agencies can create administrative delays. Approval of two products developed by Genetech for use on cattle was delayed for over a year because of a jurisdictional dispute between the Department of Agriculture and the FDA (Rhein, 1985). To ease potential conflicts, the Reagan Administration has been attempting to define more clearly regulatory authority and streamline the regulatory process.

Applications of the Art

On April 7, 1985 it was reported that researchers at the Cetus Corporation had succeeded in splicing and cloning the human gene for the protein tumor necrosis factor, or TNF (Jonesboro Sun, 1985). It is hoped that this protein, produced naturally in the human body in small quantities, can be used to attack malignant cancer cells while leaving healthy tissue unharmed. The first human trials of TNF are expected to begin in early 1986. The prospects for successful TNF use appear good, although previous laboratory products (e.g., interferon - a virus-fighting substance) have proved unsuccessful in stopping the spread of cancer.

The Cetus Corporation's TNF is just the latest in a number of increasingly frequent announcements of biotech breakthroughs. The process began in the 1950s when James Watson and Francis Crick discovered the structure of DNA. In the 1970s, when scientists first succeeded in splicing foreign genes into a ring of DNA, genetic engineering was underway.

Applications of genetic engineering are numerous, varied, and quite amazing. A simple gene-spliced bacterium, when placed in a fermentation broth, can produce more than a billion copies of itself in 15 hours. This growth rate can be contrasted with, for example, the normal method of insulin production. Prior to 1982, to supply diabetics in the U.S. with insulin the pancreata of over 80 million cows and pigs were needed yearly. In 1982, insulin produced via recombinant DNA methods was approved for sale in the U.S. and Great Britain.

Products developed by using recombinant DNA techniques have entered the marketplace in increasing numbers over the last decade. The following is a partial list of current recombinant DNA product areas:

*vaccines - largely restricted to animal vaccines, although work is nearly completed on a type designed to fight human cancers associated with viruses;

*hormones - including human insulin, a growth hormone to fight human dwarfism, and a growth hormone for cattle;

*bacteria - designed to protect plants from frost or crops from damaging pests;

*enzymes - including rennet, used in making cheese.

The aforementioned applications of biotechnology, although obviously noteworthy, have not stirred the same level of controversy as those which relate to human medicine.

In the summer of 1980, Dr. Martin Cline attempted to cure two persons suffering from thalassemia - a fatal blood disease related to sickle-cell anemia - by inserting normal hemoglobin genes into these patients' bone marrow. The surgery was not successful, having no effect positive or negative. Moreover, the operations were performed in Italy and Israel, because approval for the surgical technique was denied in the U.S..[5] As a result of Dr. Cline's activities, he was forced to resign as Chief of Hematology/Oncology at UCLA, and lost two federal grants worth more than $190,000 (Sun, 1981).

The unsuccessful attempt at human gene therapy has renewed debate regarding the technique. Potential applications of gene therapy in humans abound. Single gene mutations, the first logical targets of gene therapy, are known to cause as many as 2000 human disorders (McKusick, 1982). A defect in just one gene - cells have as many as 100,000 genes - can have fatal consequences.

Existing traditional treatments of genetic disorders are aimed at modifying or easing the damage caused by defective genes. Gene therapy is concerned with curing the disorders, not treating the symptoms. This is accomplished through the insertion of a normal gene into the cell where the defective one is active, therapy attempting to supplant the mutant gene's activity. Gene surgery would take the additional step of surgically removing a defective gene and inserting a normal one in its stead.

Gene therapy, as discussed, would involve only alterations to somatic cells, or those comprising parts of the body other than germ cells. The

reproductive (sex) cells in humans, either sperm or egg, are the germ cells. In theory, then, gene therapy would not affect a change in a patient's offspring. A child would inherit characteristics, including defects, independent of the performed therapy. The same gene therapy performed on a parent would possibly be necessary for the parent's child. One solution for this scenario would involve the most controversial of all genetic technologies, which entails altering germ cells or fertilized eggs.

Several recent laboratory developments have involved genetic manipulation of germ cells (Mark, 1981; Palmiter, Chen, and Brinster, 1982; Brinster, et. al., 1981). In one experiment, fertilized mouse eggs were injected with rabbit hemoglobin genes. The developed offspring were reported to contain rabbit hemoglobin in their red blood cells (Wagner, et. al, 1981). This approach could be applied to fertilized human eggs through in vitro fertilization techniques.[6] Accordingly, human defects could be identified, isolated, and corrected, all before the child is "born". As the fetus develops it would not contain the mutant genes nature otherwise would have provided.

Issues/Analysis

The manufacture of pharmaceuticals and other products via recombinant DNA technology is a reality.[7] The NIH's recombinant DNA Advisory Committee has indicated recently that it might be ready to approve gene therapy applied to human patients (Bishop and Waldholz, 1985). And experiments continue on the alteration of germ cells and fertilized eggs of laboratory animals. These related, but distinct, areas of technology are generating considerable debate. The following discussion will identify and examine some of the major questions being posed by experts and laymen. The issues surrounding genetic engineering fall into two categories: those regarding unforeseen deleterious effects of the new technologies, and ethical concerns that must be addressed even if the techniques work as desired.

Examples of ill-advised human manipulation of the environment are numerous. The kudzu vine, gypsy moth, and Dutch elm disease created problems that could have been avoided with foresight. Chemical engineers of the 1920s did not conceive of acid rain as a problem, while few physicians in the 1940s were concerned about the effects of low-level radiation exposure. And scientists, chemists, and product engineers today are imperfect in their efforts to keep unsafe products and chemicals off the market and out of food. Critics contend that genetic engineering is a field of great uncertainty, since scientific research often leads into

unanticipated areas. They conclude that a ban on experiments is necessary to protect society from unanticipated catastrophies.

The cited problems are real, but they do not support a ban on genetic engineering. Despite past setbacks, scientific advances have impoved greatly life over the past fifty years. Extensive government regulations presently in place are very protective and restrictive. Furthermore, problems with genetically engineered products over the last decade have been nonexistent. After all, genetic engineering only accelerates a process that occures randomly without human intervention. In nature, bacterial bits of genetic material commonly are transferred between species.

Persons should not place their collective heads in the sand when recombinant DNA technology is applied. But the issue becomes a question of burden of proof. Critics would require scientists to prove that their procedures are completely safe before they proceed. Such proof is, of course, rarely possible. Rather, the burden of proof must be placed on those opposing genetic engineering. The potential benefits from technologies such as recombinant DNA are enormous. And the scientific community generally agrees the techniques are safe. To stop the advance of knowledge, without first identifying specific dangers, is undesirable and unworkable.[8]

Of a different nature are concerns about "man" playing God. Humans are composed of the same DNA molecules as all other living organisms. Will persons lose their sense of self when they start manipulating the building blocks of life? A line must be drawn between changes in somatic cells and germ cells.

Gene therapy on somatic cells, replacing defective genes with normal funtioning ones, is simply an extension of the surgical techniques practiced for the last century. A defective portion of the body is repaired or replaced, albeit through a very sophisticated surgery. Accordingly, questions should focus on the effectiveness of gene therapy and not on its desirability as a medical technique. Regarding the notion of "man" playing God, the following question is relevant: Is it God-like to deny therapy to persons suffering greatly from sickle-cell anemia or cystic fibrosis?[9]

An entirely different area of concern involves changes in germ cells or fertilized eggs. One could ask whether it is better to remove mutant genes from a germ cell, or wait until a child is born defective?

Theoretically, it is better to avoid a problem. In practice, however, it would be very difficult to identify and isolate defective genes at that stage. And morally, there are many unanswered questions about such a procedure.

For example, what is a defect? Are low intelligence and unattractiveness defects? Should selection of hair color or body size be allowed if this were possible? Would Beethoven have been a better person and musical composer if his hearing and eyesight problems had been genetically corrected before birth? These questions are difficult, and a consensus on appropriate answers is lacking. Near perfect chances for success would be required before genetic surgery could be attempted. Society would not accept an 80 or 90 percent success rate on the manipulation of germ cells, for such surgery could possibly damage unborn children.[10]

Conclusion

Over the last several decades, humankind has been obliged to reconcile the desire for knowledge with the survival of the human species. With advances in knowledge, persons now have the ability to either destroy themselves or provide beneficial services for society. If properly applied, the science of genetics will fall into the latter category, thereby offering a great tool for human betterment.

Yet scientists must be concerned constantly with potential pathogens, or those organisms that could be converted, with a few mutations, from something harmless to a serious menace. But scientists are properly cautious, due in large part to elaborate government regulations. The probability of major unintentional damage being inflicted upon humankind through genetic engineering is very small. Intentional misuses of genetic technology are probable, as the world will always produce a number of Hitlers. However, the fear of potential abuse alone should not stop the pursuit of beneficial knowledge and technologies.

The issue surrounding the genetic alteration of germ cells, or fetilized eggs, has a different character. The profound nature of gene splicing, as applied to unborn individuals, requires the attention of all citizens. This is particularly important because present regulatory efforts in this area are not sufficient. The whole of society, not just scientists and administrators, must be involved in deciding how this

technology shall be used. Public education efforts should be increased, while a committee with oversight authority should be convened. This committee would draw membership from scientists, religious and academic leaders, lawyers, doctors, and members of the general public. For now that humankind has the tools of science, they must not be used to destroy the world.

Most important is that humans must not become enamored by technology to the extent that moral and ethical questions are obscured. Nowadays the tendency is to move ahead with programs simply because they are technologically possible. Technology, in other words, cannot answer questions that only humans can pose. For at the root of technology is human action that cannot be obscured if this tool is to be used correctly.

FOOTNOTES

1. Humankind has always struggled with, and at times fought against, advances in technology. The issues addressed by this paper, though, represent a leap from issues raised by previous changes in knowledge. Challenges to the medical technologies of 1985 cannot be attributed solely to humankind's inherent resistance to change.

2. Prior to Mr. Clark's operation, the federal government had spent over $200 million aiding research in the development of artificial (mechanical) heart technology. To purchase an artificial heart, $100,000-$200,000 is needed for the operation and first year service alone. These facts, and others, give rise to a number of areas of controversy, including the following:

*Should an artificial heart be denied to a patient based on his or her ability to pay? The taxpayer has already funded a portion of his/her bill by contributing to the research vis-a-vis tax payments.

*Should any life-giving technology be denied a patient based on financial considerations? When the dialysis machine became a perfected technology, treatment was partially restricted to those able to bear the costs involved. This restriction has all but disappeared. Will the same evolutionary process affect new medical technologies and, if so, where will the money be found to pay for the treatment provided?

3. The term "genetic engineering" was first used by Rollin D. Hotchkiss, "Portents for a Genetic Engineering," 56 J. Heredity 197 (1965).

4. For a listing of the federal agencies, and a description of their powers and areas of authority, see the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Splicing Life: The Social and Ethical Issues of Genetic Engineering with Human Beings, U. S. Government Printing Office, Washington, DC, 1982.

5. Approval was denied, among other reasons, on the basis that more animal work was needed. See the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Protecting Human Subjects, U.S. Government Printing Office, Washington (1981) at 177, 182.

6. The approach would involve the following: (1) isolating and amplifying the desired gene by standard recombinant DNA techniques; (2) removing a mature ovum from a woman and fertilizing it in vitro; (3) injecting copies of the cloned gene into the fertilized egg (zygote) using microsurgical techniques; and (4) implanting the genetically altered zygote into the woman's uterus.

7. Users of recombinant DNA techniques won a significant legal battle when the Supreme Court ruled patent protection was available for new life forms created. Diamond v. Chakrabarty, 447 U.S. 303, 316 (1980).

8. Genetic engineering on biological warfare weapons is a separate issue. Drawing on recombinant DNA technology, biological weapons could conceivably be devised to eliminate selected animals, plants, or people. Despite the 1972 Biological Weapons Convention, this type of research is probably being conducted in the Soviet Union, United States, and elsewhere. Research in this area is reprehensible and should be stopped. But the problem is with the misuse of knowledge, not with the scientific knowledge itself. A ban on all genetic engineering in the U.S. would not stop such efforts elsewhere in the world.

9. There is considerable support from religious scholars for gene therapy, appropriately applied. Pope John Paul II gave his approval for gene splicing when its aim is to ameliorate the conditions of those who are

affected by chromosomic diseases. "La sperimentozione in biologia deve contribuire al bene integrale dell'uomo," L'Osservatore Romano, Rome, Oct. 24, 1982, at 2.

10. Near perfection for the surgical procedure would not be required if the following conditions could be met:

* It was ascertainable with near certainty, upon examination of the fertilized egg, the child would be born with a serious defect;

* The genetic surgery would, at worse, not improve the child's condition - it would not further damage the unborn child.

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