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GENETIC ENGINEERING

EVOLUTION OF A TECHNOLOGICAL ISSUE

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REPORT

TO THE

SUBCOMMITTEE ON SCIENCE, RESEARCH,  
AND DEVELOPMENT

OF THE

COMMITTEE ON SCIENCE AND ASTRONAUTICS

U.S. HOUSE OF REPRESENTATIVES

NINETY-SECOND CONGRESS

SECOND SESSION

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## LETTER OF SUBMITTAL

THE LIBRARY OF CONGRESS,  
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Washington, D.C., November 8, 1972.

Hon. JOHN W. DAVIS,  
*Chairman, Subcommittee on Science, Research, and Development, Science and Astronautics Committee, U.S. House of Representatives, Washington, D.C.*

DEAR REPRESENTATIVE DAVIS: I am pleased to submit this review of the status of research in genetic engineering at your request. The study is responsive to the widespread concern both in the Congress and among the public generally as to the far reaching implications of this branch of modern science.

The study was prepared by Dr. James M. McCullough of the Science Policy Research Division as an analysis of some of the alternatives that might be available to society as this new science evolves. The problems considered by Dr. McCullough include both the use of genetic engineering to eliminate genetic diseases and the social control of the applications of genetic engineering. Dr. McCullough consulted with a number of research investigators during the preparation of this report. We would like to acknowledge at this time the very helpful advice and constructive criticism offered during the review of the study by Dr. Joshua Lederberg, Department of Genetics, Stanford Medical School; Dr. Leon R. Kass, Executive Secretary, Committee on the Life Sciences and Social Policy, National Academy of Sciences; and Dr. Marc Lappé, Staff Biologist, Institute of Society, Ethics, and Life Sciences, although the final responsibility rests with the author and the Congressional Research Service.

May I express my appreciation for this opportunity, on the part of the Congressional Research Service, to cooperate in the preparation of this study of a subject of such far reaching and serious social significance.

Sincerely,

LESTER S. JAYSON,  
*Director, Congressional Research Service,  
Library of Congress.*

(III)

LETTER OF SUBMITTAL

The following is a list of the names of the authors of the papers submitted for consideration for the award of the Nobel Prize in Physics for the year 1902. The names are given in the order in which they appear in the list of contents of the volume. The names are given in the order in which they appear in the list of contents of the volume. The names are given in the order in which they appear in the list of contents of the volume.

Director of the Institution  
Stockholm, Sweden

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# GENETIC ENGINEERING

## Evolution of a Technological Issue

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### I. INTRODUCTION

#### *Purpose*

The purpose of this study is to: (1) review the status of research in genetic engineering and closely related fields of study; (2) identify the developing issues and their potential impact; and (3) report on recent efforts to provide for investigation and evaluation of these developments.

#### *Genetic Engineering*

Genetic engineering is a broad field of biomedical research about which there is an increasing amount of criticism and concern. The concern is unusual, for the most vocal and critical reaction is coming from within the biomedical research community and from the ethicists and philosophers, and not, as yet, in a concerted fashion from the general public. This may be due in part to a lack of understanding on the part of the public; it is certainly not due to a lack of publicity for there has been considerable discussion of genetic engineering in the scientific and religious journals as well as the general news media.

An analysis of the developments in genetic engineering is complex for there has been a tendency to collect several important areas of biomedical research within this terminology. In the field of embryology, or the study of the growth of the fertilized egg to maturity, several important advances associated with the reproductive process have evolved and these new techniques have produced considerable tension among biologists in the past few years. The molecular biologists have continued the careful, precise, and methodical disassembly of the strands of life controlling substances known as chromosomes and have had some success in the reconstruction of these important molecules in the laboratory. At the same time, the cell physiologists and biochemists have been learning new approaches for disassembling and reassembling cells and in the process are opening the door to direct intervention in the heredity of the cell. In other fields, biomedical scientists have been turning to more intensive study of the effects of the interaction of heredity and environment.

The subject of genetic engineering has been discussed from so many different viewpoints that it is not a simple task to furnish a precise definition of the term. Genetics, of course, is the science of heredity. Engineering involves the practical application of the knowledge developed within a science such as biology. Genetic engineering should mean simply the engineering of heredity. But there are so many techniques which can affect heredity that the actual scope of the term

“genetic engineering” has been broadened in many discussions. In the most precise considerations, genetic engineering has been defined as:

The change of undesirable genes to more desirable forms by a process of directed mutation.<sup>1</sup>

The prospect of being able to insert, deliberately, specific factors (genes) into the genetic material.<sup>2</sup>

The direct manipulation of the genetic message by changing, subtracting, or adding to the instructions received by the cell.<sup>3</sup>

All these definitions or explanations indicate that the scope of genetic engineering frequently includes those aspects of molecular biology which are concerned with controlled change, in some way, of the gene material within the nucleus of the cell. As all cells produced by the genetically modified cell will contain the change as a result of chromosome duplication, this type of genetic engineering may have an influence not only on the immediate development of an individual but also upon the progeny produced by that individual. The intent is to effect genetic changes to eliminate known genetic defects, such as the metabolic diseases, or for the improvement of desirable traits such as the inheritance of intelligence.

In his paper, “On Redoing Man—The Ethics of Genetic Engineering,” Kurt Hirschhorn has included such topics as artificial insemination, genetic counseling, eugenics (manipulation of the environment to affect development), positive and negative eugenics, genetic diagnosis, and control of fertility.<sup>4</sup> Other authors take a similar broad view of the subject. In a recent editorial within the *Journal of the American Medical Association*, the comment is made that:

The popular term, genetic engineering, might be considered as covering anything having to do with the manipulation of the gametes or the fetus, for whatever purpose, from conception other than by sexual union, to treatment of disease in utero, to the ultimate manufacture of a human being to exact specifications. It has nothing to do with the creation of life; it is concerned only with the method for transmitting life \* \* \* Thus, the earliest procedure in genetic engineering \* \* \* is artificial insemination, next \* \* \* artificial fertilization \* \* \* next artificial implantation \* \* \* in the future total extracorporeal gestation \* \* \* and finally, what is popularly meant by genetic engineering, the production—or better the biological manufacture—of a human being to desired specifications.<sup>5</sup>

Whatever term is favored for these topics collectively, or through some other scheme of classification of the various related developments this paper discusses genetic engineering to include the spectrum of

<sup>1</sup> Donald Huisinck, *Should Man Control His Genetic Future?* *Zygon*, vol. 42, Feb. 1969), p. 189.

<sup>2</sup> Gordon Rattray Taylor, *The Biological Time Bomb* (New York, World Publishers, 1968), p. 159.

<sup>3</sup> I. Michael Lerner, *Heredity, Evolution, and Society* (San Francisco, W. H. Freeman Co., 1968), p. 273.

<sup>4</sup> Kurt Hirschhorn, *On Redoing Man—The Ethics of Genetic Engineering*, *Commonwealth*, May 17, 1968, pp. 257–261.

<sup>5</sup> *Genetic Engineering: Reprise*, *Journal of the American Medical Association*, vol. 220, No. 10, June 5, 1972, pp. 1356–1357.

knowledge associated with the topics of artificial insemination, cloning (culturing from a cell or group of cells), in vitro fertilization (fertilization made to occur experimentally away from the organism), molecular genetics, genetic counseling, medical genetics, eugenics (improvement of the quality of a race), and environmental factors affecting heredity.

There is good reason for much of this generalization in the use of the term "genetic engineering." Many of the advancements in molecular biology are producing rapid progress in all aspects of genetics, and also are providing the basic information required to solve other related problems in the life sciences. An expansion in capabilities to detect, identify, and possibly modify, genetic defects in-utero has already affected the course of action in genetic counseling.

The specific differences in the various topics should be kept in mind, however, in order to better understand the rate of progress and to place the implications of new developments in proper perspective. A breakthrough in one area, such as in vitro fertilization of the human egg, opens up new possibilities in such areas as artificial insemination and the accessibility of the gene to direct synthesis or change. Genetic counseling, a long established procedure and generally accepted technique, is being influenced by the new, and somewhat controversial, developments in the early detection of genetic disease. Progress in some areas, such as commercialization of sperm banks, may require government intervention while the practice of artificial insemination generally is conceived as involving private judgment and assessment. Each of these various topics is treated in more detail in the sections which follow.

The studies in genetic engineering are exciting to the biomedical scientist because the knowledge being gained will profoundly influence many current procedures for the treatment of infertility and other reproductive deficiencies. In addition, some of these same new techniques may permit the physician to correct genetic errors and prevent many serious diseases—and preventive medicine is increasingly being recognized as a most desirable approach to the solution of the health care dilemma. There has been perhaps an unfortunate tendency for the popular literature in reporting progress in genetic engineering to highlight the interest arousing and concern-stimulating events by utilizing such phrases as "fabrication of man", "cloning of man", "surrogate mother", "man-beast hybrid", "test-tube baby", "creation of life", and "carbon-copy human". One side effect of the use of such terms has been some distortion and obscuration of immediate and beneficial products of these events by an emphasis on the long range potential for harm to society.

Serious problems are connected with the progress in certain fields of genetic engineering just as there have always been controversial issues associated with significant new capabilities in medicine. Society still struggles for a solution to the ethical and legal debates associated with the new organ transplant techniques. The very definition of life and death is a topic being evaluated in our highest courts because of new medical capabilities. Beyond even these topics of concern, however, genetic engineering is being referred to as providing a potential for political abuse which is unique in our history. This is a serious charge not to be lightly disregarded. Every stage of civilization has

been exposed on many occasions to undesirable and dangerous political controls. The current political atmosphere in the world is no exception. It does not appear immediately evident, however, that prohibition of scientific developments is the way to prevent the abuse of these scientific capabilities for politically motivated purposes. On the other hand, events in history have produced a growing recognition of the need for caution in the introduction of new technological capabilities.

### *Scope of the Study*

A description of the significance of the work in genetic engineering would be difficult without providing some knowledge of the burdens which the geneticist is attempting to correct or prevent. The physician knows first hand of the chromosome abnormalities which produce mental retardation requiring lifetime institutional care. So do the families of these unfortunate children. The physician and affected families also are familiar with the crippling and lethal effects of inherited diseases such as sickle cell anemia (a blood disease) and Tay-Sach's disease (an inherited metabolic disease). The disappointment of the infertile male or female is a strong incentive for research on reproductive physiology.

This report provides background information on the progress in and application of genetics in such areas as counseling and medicine. The new knowledge and skills which are evolving in gene therapy and control of the reproductive process are described. The issues are summarized and the attempts to deal with these issues by institutions and government are discussed. The report is not intended to be an exhaustive review of all of the scientific research associated with genetic engineering. For example, many of the advances in plant hybridization—the so-called Green Revolution—have contributed significantly to the alleviation of hunger and malnutrition. Even here, however, controversies may be noted for these developments in agriculture are viewed with mixed feelings by many students of world ecological problems. In a similar fashion, the priority being placed on the alleviation of fertility problems in human beings is questioned because of the current emphasis on liberalizing abortion and the general need to control population growth.

### *The Extent of the Problem in Human Genetics*

Estimates of the incidence of genetic disease have been compiled by a number of investigators and in some instances, are very accurate. This is particularly true for specific diseases which have been carefully described and studied in a precisely identified population. The differences in the values of the various estimates cited in this report are a reflection of the absence of accurate comprehensive data on the incidence of all inherited defects as well as the difficulty in classifying genetic defects. For example, congenital defects exist at birth and may or may not be due to a hereditary defect. About 5 percent of all babies born in the United States have some kind of congenital defect. This means that about 45 to 50 of every 1,000 newborns will have a defect due to an error in the genetic message or due to some imperfection produced by the prenatal environment; for example, the effects of a disease such as rubella may interfere with normal development. These data are not equivalent to the estimates which describe the incidence of life-threatening genetic disease in newborns. Genetic disease

may be congenital but all congenital disease is not genetically determined. More explicitly, congenital disease has been defined as:

Existing at, and usually before birth; referring to conditions that are present at birth regardless of their causation.<sup>6</sup>

Other statistics cite data on genetic disease which occurs in accordance with carefully defined "genetic principles" and do not include data on diseases which may not be adequately described by these particular principles. The influence of environment, both prenatal and postnatal, further complicates the problem of determining the genetic character of some diseases. Some estimates include only disorders of certain types, for example, serious life threatening disorders, while other estimates consider all genetic disease. In many instances the data do not clearly designate the categories of genetic disease which have been compared.

The term "trait" or "character" is used in genetics terminology to refer to any detectable property of an organism whether it be hair color, height, or the absence of an essential enzyme. As best as can be determined within the almost infinite variety of human characteristics, any deviation from the normal trait as a result of a change in the genetic material may be referred to as a genetic aberration. If a change in a trait produces a pathological condition, it is usually referred to as a genetic disease. In some instances, however, a genetic defect may not seriously interfere with the functioning of an individual within society and thus the incidence of this defect might be disregarded in some estimates. Occasionally, it is not clear that a given defect is distinct from a different designation given by another investigator.

Although a comparison of the estimates of the incidence of genetic defects may be confusing because of the absence of a strict correlation between estimates, a trend can be distinguished. The incidence of genetic disease is significant, by any estimate, and as more data are accumulated the older estimates are being shown to be quite conservative. Better data are required on the incidence of genetic disease.

More than 1,500 genetic defects have been cataloged and new genetic defects are being described in increasing numbers. Some of these defects are due to direct inheritance of a preexisting defect handed on from parent to child and some are new defects caused by radiation, chemicals or other environmental factors.

The cost to society of genetic disease is significant in many instances and, since medical care is improving, the incidence may increase as a result of survival to reproductive age of individuals with these genetic defects.<sup>7</sup> For example, some statistics frequently cited indicate that:

Five women with Wilson's disease, a formerly fatal defect of copper metabolism, are alive and well in the Midwest and two have borne children.

About 130,000 diabetic women are now of an age to reproduce.

One infant of every 1,000 to 2,000 live births has cystic fibrosis.

<sup>6</sup> L. R. C. Agnew, et al. *Dorlands Illustrated Medical Dictionary*. (Philadelphia, W. B. Saunders Company, 1965), p. 336.

<sup>7</sup> R. Rodney Howell and Roger E. Stevenson, *The Offspring of Phenylketonuric Women*, *Social Biology*, vol. 18, Supplement, Sept., 1971, pp. S19-S29.

One of every 600 U.S. newborns is afflicted with Down's syndrome (Mongolism).

Conservative estimates state that 10 percent of all admissions to U.S. pediatric services are due to genetic defects.

Of the mental retardates in institutions today, 5 percent have inborn errors of metabolism, 10 percent suffer from Down's syndrome, and 25 percent have central nervous system defects, many of which are inherited.<sup>8</sup>

Another estimate of the extent of genetically induced birth defects indicates that more than 2 percent of the population suffers from diseases or defects which are inherited according to Mendelian laws.<sup>9</sup> Another 5 percent have disorders in which both environment and heredity tend to be associated with the development of the disease. Within the population of the United States, these numbers would indicate that more than 10 million people are adversely affected by genetic factors (the National Institute of General Medical Sciences has estimated that more than 15 million Americans are affected).

The cost to society for these defects has never really been evaluated but occasional estimates give some order of magnitude. For example, Dr. John W. Littlefield of Massachusetts General Hospital and Harvard Medical School has been reported as stating that "the care of 54 mongoloid infants that we estimate were born to Massachusetts mothers in 1968 will eventually cost this State at least \$3,240,000."<sup>10</sup>

1972 The cost for the 3,000 mongoloids now in institutional care has been estimated at about \$180 million for lifetime care. Other estimates indicate similar or greater cost for undetected and untreated genetic disorders. In Oregon, for example, costs for detecting 24 children with inherited metabolic disorders over a 9-year period were estimated at \$49,000 per year. Total savings as a result of prompt detection and treatment were in excess of \$5.6 million for the life of the individuals. Other ratios for the various types of serious defects indicate a range from about 1 in 400 births for sickle cell anemia to about 1 in 330,000 births for some of the rare defects; on the average, it has been estimated that 1 in 250 babies has some serious genetic defect.

As each of the more than 1,500 defects may require a specific type of medical care or treatment, the task of controlling genetic defects by medical treatment seems endless. The challenge is great to do something. But what should be done? Improved detection of carriers? Increased abortion of defective fetuses? Genetic manipulations? The rewards could be enormous; not only in economic savings but in the relief of the tremendous emotional burden associated with the birth and care of many of these defective children. The prospects are slight that many of the 1,500 diseases will be amenable to genetic manipulation in the near future. A dilemma is that the ability to treat or cure genetic disease results in the availability of knowledge which has an even greater potential impact for the manipulation of the hereditary traits of all men. In addition, medical scientists are converging on the cellular level of human experimentation where past experience provides little guidance. This latter problem in particular is producing the immediate demand for careful consideration of the ethical, legal, and social effects of new developments in genetic engineering.

<sup>8</sup> Genetic Control—Threat or Therapy? Medical World News, May 5, 1972, pp. 45-55.

<sup>9</sup> Ernest Freese. Prospects of Gene Therapy. Science, vol. 175, March 3, 1972.

<sup>10</sup> Medical World News, *op. cit.*, p. 46.

## II. GENETICS—HISTORICAL OVERVIEW

### *Mendelian genetics*

The basic rules governing the transmission of hereditary traits were introduced by a monk named Gregor Mendel. His studies, the foundation for modern genetic engineering, were published in 1865.<sup>1</sup> This work was at first essentially ignored. A major reason cited for the disregard of Mendel's work was the fact that other areas of science had not advanced sufficiently to provide the insight into his work required to appreciate its significance. For example, research in cell physiology had not progressed sufficiently to provide the required knowledge about cell division processes. Prior to the work of Gregor Mendel, one of the more frequently encountered explanations for the inheritance of traits was a blending theory. This concept of inheritance suggested that factors which control inheritance are blended, as in the physical mixing of blood from two different individuals, and, once the blending has taken place, no separation of traits can occur. Down through the generations, more mixing and blending produces the degrees of differences which are observed among individuals.

Mendel presented the new and unifying concept that the inheritable traits are controlled by pairs of discrete unit factors, contributed one from each parent, and these units are passed on unchanged in form from generation to generation. He also demonstrated the idea of dominance and recessiveness. For example, Mendel crossed a plant having a certain trait (tall) with a plant of the same species having the opposite characteristic (short). When a genetic factor for a trait exists in more than one form, in this way, the different forms are called alleles. Thus, tall is an allele of short. The offspring from this cross were all tall. The term "hybrid" is used to designate the offspring from parents differing in one or more traits.

Mendel referred to the trait that appeared in the hybrid (tall) as the dominant character and the trait concealed (short) recessive. He then crossed the hybrid plants and noted that both tall and short plants were present in the next generation. This observation indicated that the recessive trait had not been modified in the hybrid but had been concealed and passed on unchanged in influence. Mendel explained the inheritance of height in the plants by suggesting that the dominant and recessive traits (alleles for height) are separated during the formation of eggs or sperm (the sex cells) and then recombined, at random, in the new progeny. His careful observation of the numbers of plants of each height in each generation supported the theory of random recombination and contributed to the modern techniques of statistical analysis associated with genetic counseling.

The fertilized egg (the zygote) develops with the trait for height determined by the unit factors received during the fertilization. If

<sup>1</sup> Gregor Mendel. *Experiments In Plant Hybridization: With Commentary and Assessment* by Sir Ronald A. Fisher. (London, Oliver and Boyd, 1965). 95 p.

the alleles for height are alike, the new offspring are said to be homozygous and will be either tall or short. If the alleles for height are unlike, the offspring are said to be heterozygous and will be all tall as in the case of Mendel's experimental plants. The physical appearance (phenotype) for a particular trait (height, for example) thus depends upon the manner of recombination of the unit factors (genotype) controlling the trait. Mendel's experiments revealed that one member of a pair of unit factors might conceal or dominate the expression of the other member of the pair. An important point is that the recessive unit factor in the hybrid, even though not expressed in the appearance of the hybrid, is still available to be passed on to the next generation. Two recessive unit factors, one from each parent, will produce the phenotype (appearance) for the trait (a short plant in the example cited); one dominant and one recessive or two dominant alleles result in a dominant phenotype (tall).

Mendel had hypothesized that each parent must contribute in the sex cell one-half of the pair of heredity factors (alleles) in random fashion, that is on a 50-50 by chance basis. Subsequent research on the cell division process by which sex cells are formed (called meiosis), revealed that within the nucleus of the cells of the sex organs, ovary or testis, specific paired structures called chromosomes were separated in such a fashion during cell division that only one chromosome from each pair was transmitted to an egg or a sperm. Chromosomes are elongate, threadlike bodies in the nucleus of a cell clearly visible when the cell is dividing. For example, in human body cells, which normally contain 23 pairs of chromosomes, the sperm or egg was found to contain only 23 chromosomes—one chromosome from each pair. This is the physical evidence for Mendel's hypothesis that one-half of a pair of heredity factors were being transmitted on a 50-50 chance basis.

However, in the case of the development of a new multicellular organism from a zygote (the fertilized egg), an increase in size is produced by an increase in the number of cells. This increase in number of cells occurs by a different type of cell division called mitosis. In mitosis, the chromosome pairs are not separated during cell division but are replicated in such a way that each new cell gets the same number of chromosomes each time a cell divides. In this way, each cell of the body (somatic cell) maintains a complete set of chromosomes identical with the parent cell. Thus, the sex cell has one-half of each pair of a set of paired chromosomes (the haploid number of chromosomes) while somatic cells have a full set of paired chromosomes (the diploid number). The union of two sex cells with the haploid number of chromosomes produces the zygote with the diploid number of chromosomes.

The processes of mitosis and meiosis provide the mechanism for maintaining a constant number of chromosomes in each generation—meiosis producing a reduction in chromosome number in the formation of sex cells; fertilization resulting in restoration of the diploid number of chromosomes; and mitosis maintaining the diploid number. If this cycle of meiosis and mitosis did not occur in a sexually reproducing organism, the number of chromosomes would double in each generation during each fertilization and the total number of chromosomes would approach infinity. The two processes of cell division are important in genetic disease for errors during the cell division processes can produce physical defects with different meaning from the stand-

point of genetic counseling. In some instances defects will be produced in an individual during mitosis but will not be transmitted to succeeding generations. This point will be clarified in the discussion on genetic counseling.

Mendel's unit factors, called "genes" by modern geneticists, are now known to be located on the chromosomes. An explanation for his observations of the separation of unit factors during reproduction and the chance recombination in the formation of new progeny is possible on the basis of: (1) the cell division process of meiosis in which the chromosome pairs are separated; and (2) fertilization in which the chromosomes are recombined in pairs.

The modern geneticist also found explanations in the processes of meiosis and mitosis for many inherited and noninherited somatic (body) abnormalities. Various types of chromosomal aberrations are known to result in a malfunction of genes. Such malfunctions may be fatal to the organism or may result in some less serious effect or function. These aberrations include events such as:

- (1) crossover, in which genetic material is exchanged between chromosomes;
- (2) deletion, in which sections of a chromosome are lost during the cell division process;
- (3) nondisjunction, in which the chromosomes fail to separate so that one cell gets extra chromosomes and another cell does not get the chromosomes involved;
- (4) duplication, involving an increase in the number of genes on a chromosome;
- (5) inversion, in which the arrangement of the genes on a chromosome is changed.

These chromosome abnormalities, together with the spontaneous formation of defective genes, offer a physical explanation for many of the inherited diseases. Any change in the genetic substance resulting in a new characteristic which may be passed on to the offspring is a mutation. The mutation may be due to a change in the chemical makeup of the gene or may be due to a change in the structure or arrangement of the chromosomes. Mutations are usually recessive and harmful to the organism. The reason is that the species is the product of a long period of evolution. The more efficient phenotypes have survived exposure to the selective forces of the environment. The chance that a sudden mutation will be more efficient is less likely than the chance that the change will be harmful. Most mutations are recessive; however, it is possible for a mutation to be dominant and beneficial. Nevertheless, there are more harmful recessive mutations occurring within a population than there are dominant, beneficial mutations. The genetic engineer has as a major task the development of techniques to correct genetic defects which interfere with the functioning of the individual within his environment.

### *Biochemistry of Heredity*

The basic molecule of the chromosome which controls the activities of the cell is a long, coiled structure called deoxyribonucleic acid (DNA).<sup>2 3 4</sup> The DNA found in each chromosome is divided into the

<sup>2</sup> Erwin Chargaff. Preface to a Grammar of Biology. Science, vol. 172, May 14, 1971, pp. 637-642.

<sup>3</sup> James D. Watson. The Double Helix. (New York, Athenum, 1968.) 226 p.

<sup>4</sup> Lawrence P. Lessing. DNA: At the Core of Life Itself. (New York, the MacMillian Co., 1967.) 85 p.

small units called genes which provide the code for the synthesis of intermediate or messenger molecules of ribonucleic acid (RNA). RNA guides the synthesis of many different enzymes and other proteins. The collective action of thousands of genes under elaborate chemical control produces the many responses which are evidenced as growth, development, and the life activities of an organism. When the genes do not function, function improperly, or are missing or blocked in some way, defects may be expressed in the form of disease or altered physical structure.

The geneticist, with the rather considerable assistance of the molecular biologist, has learned a great deal about the way the genes exercise influence within the cell. As the substitution of even a single atom in an enzyme may change the characteristics of the molecule in such a way as to affect the physiology of an entire organism, a very high order of sensitivity is essential to the regulatory activity of the gene. Mistakes in synthesis do occur occasionally in the assembly of the molecules of life. These errors are numerically quite small in terms of a total population, although the mistake can be quite serious for an individual.

Most of the research completed in efforts to understand the chemical structure and specificity of DNA has been accomplished with bacteria and viruses. These organisms have relatively simple DNA and reproduce in such large numbers in a short period of time that population studies are conducted quite easily. In addition, the relatively small number of genes on the DNA of certain viruses permits exact identification of the code. The knowledge now available on DNA structure suggests that the fundamental nature of DNA is the same whether it is found in viruses or man. The varying arrangement of the coding units and the quantity of DNA produces the differences in the various organisms.

A number of factors can cause a change in either the expression of a gene or a physical change in the structure of the gene. Some of these factors are X-rays and ultra violet radiation, many different kinds of chemicals in the environment of the cell, viral or bacterial infections, and abnormal division processes during mitosis or meiosis (as previously noted). When changes in gene structure are permanent, a mutation is formed and the change will be passed on to all cells produced by the changed cell. If the change occurred within a sex cell or within a cell which produces sex cells, then the new progeny may show the effect of the change and the change will be inherited. Recessive mutations may be concealed by dominant genes and thus fail to be immediately identified.

As new techniques have evolved, the molecular biologist has been able to delve deeper and in greater detail into the fine structure of the cell. It is now possible by advanced microtechniques to remove a nucleus from a cell and transfer the nucleus to another cell. Precise techniques permit the biochemist to examine the fine structure of DNA, enzyme systems, and other aspects of cell biochemistry as well as providing the opportunity to separate and duplicate extremely small sections of the DNA molecule. Investigations with bacteriophages, the viruses which infect bacteria, have provided information on the procedures which permit the transfer of DNA units from one

cell to another. Synthesis is now feasible for many of the less complex hereditary units. These developments, along with the significant advancements in theoretical ideas, have permitted rapid progress in the biological sciences in much the same way as the discovery of the atomic theory and the associated technological developments facilitated advancements in nuclear physics.

### *Human Genetics in Brief*

Human genetics, as a science, is concerned with the way in which the hereditary units are passed on to succeeding generations, with the factors which may change the characteristics of the genes, and with the way the expression of the genes is affected by the environment of the individual. Human genetics poses a real problem in analysis, for the experimenter works with essentially uncontrolled populations. The principle of experimental work usually demands carefully defined standard populations and this is the way that genetics experiments are conducted with animals and plants. In studying inheritance in man, however, the experimenter lacks control, has difficulty in obtaining valid historical data, and works with a relatively long-lived organism with a small number of progeny per generation. Nevertheless, by dealing with population data, by sharing information with other workers throughout the world, and by many new and refined methods of large-scale sampling, the modern geneticist has collected a great deal of information about the inheritance of traits in man.

The biological basis of inheritance in man is the same as it is with other sexually reproducing organisms. The new individual receives his inheritance from each parent. The male contribution is made through the sperm, the female contribution through the egg. Union of these two sex cells provides the new, normal, individual with 23 pairs of chromosomes, one chromosome of each pair from each parent. Each of these chromosomes in turn contains a large number of individual units or genes which will control specific functions within the developing individual.

Many genetic hazards precede and accompany the course of development of the new individual. These hazards may produce changes in the chromosomes or genes which in turn may adversely affect the immediate development of the individual or later in life. Some of these hazards occur when the chromosomes are damaged or fail to separate precisely. The failures can occur during the formation of the egg or sperm, during fertilization, or during subsequent early division of the fertilized egg. These so-called chromosome abnormalities produce specific types of defects; some prevent normal development and result in spontaneous abortion and others do not result in abortion but produce a human being with some defect. The number of visible chromosome abnormalities has been estimated to be as high as 4 to 5 out of every 1,000 live births.<sup>5</sup> Included among the more commonly occurring chromosome abnormalities are the genetic defects known as Down's syndrome (mongolism) (trisomy of chromosome 21) and Edward's syndrome (causes death in infancy) (trisomy of chromosome 17 or 18). Other chromosome abnormalities are associated with a greater or lesser number or quantity of chromosomal material or some change in the

<sup>5</sup> F. Sergovish, et al. Chromosome Aberrations in 2,159 Consecutive Newborn Babies. *The New England Journal of Medicine*, vol. 280, April 17, 1969, pp. 850-855.

arrangement of the chromosomes. One of the major difficulties which had slowed knowledge about chromosome defects had been the problem of precisely identifying all of the different types of human chromosomes. With the advent of new techniques of staining and counting chromosomes, it is now possible to examine the chromosome content of cells, and identify the abnormality.

Another type of genetic deficiency is produced by a change of the gene or group of genes on the chromosome. Research has shown that the change of a single atom in a molecule of a gene may adversely affect the individual in some way. The change may be inherited as a dominant trait or the factor may be a recessive type; that is, usually expressed only when in a paired or homozygous condition. Examples of these gene determined differences are numerous and include sickle cell anemia (a blood disease), albinism, phenylketonuria (a metabolic disease), and hemophilia (a blood disease). A very comprehensive catalog of about 1,500 genetic defects has been prepared by Victor McKusick of John Hopkins University.<sup>6</sup>

The biochemical change of a gene structure may result in a failure to produce an essential enzyme which may lead to a change or block in a metabolic cycle. This block may result in a toxic accumulation with a resultant adverse effect on the body. Until recently, most of the research effort was directed toward identifying the precise biochemical nature of the gene change and the effect on metabolism. An attempt was then made to compensate for the change with an administration of the missing enzyme or other ingredient, for example, the provision of insulin to diabetics. With the advent of modern genetics, enthusiasm now centers around the possibility that the defective gene may be replaced by a corrected gene—the gene therapy of the future. An alternative method for controlling genetic disease involves genetic counseling of the parents who carry the defective genes so that an informed decision about parenthood might be made or therapeutic abortion might be considered. Each of these various techniques of preventing or compensating for genetic defects will be discussed more fully in later paragraphs.

#### *Environmental Factors of Concern in Genetics*

All living organisms are exposed to environmental factors which can produce mutations. Change has been occurring since the appearance of life; the geneticist is naturally interested in identifying the environmental factors which can induce a permanent genetic change or mutation. Although the chance of survival of an individual genetic change is small, some changes do persist in a population. The survival of a change (the changed individual) will be enhanced if the new trait increases the survival potential of the individual in competition within its total environment. This principle of natural selection, emphasized by Charles Darwin, is the most important aspect of our understanding of the process of evolution.

Many chemical substances are known to be mutagenic (causing a mutation) and some experience has been collected with such agents as

<sup>6</sup> Victor A. McKusick. *Mendelian Inheritance in Man. Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes.* (The Johns Hopkins Press, Baltimore, 1971). 783 p.

some pesticides, nitrosamines, liquid mustard, formaldehyde, and others.<sup>7 8</sup> In order for the gene change or mutation to be inherited, it is necessary for the mutagenic agent to effect the change in the reproductive organs and ultimately within the reproductive cells specifically. Mutagenic chemicals may accumulate within a reproductive organ as a result of faulty metabolic activities or the mutagenic chemical may be ingested and come into contact with the sex organs as a part of the digestion and circulation process.

No comprehensive data have been assembled on the mutagenic effects of chemicals on man. The evidence which is available suggests that additional care needs to be taken to evaluate the risk from the thousands of chemicals produced during industrial processes and disseminated within the environment as well as the large numbers of chemicals encountered in food and water supplies.

The most highly publicized mutagenic agent is ionizing radiation. Medical and dental devices, nuclear power reactors, nuclear weapons, and natural phenomena such as cosmic rays are all sources of X-rays, gamma rays, and charged particles which produce ionization reactions in living cells. Many forms of ionization radiation will readily penetrate living tissue and cells deep within the body may be damaged. The cells in the sex organs are particularly sensitive and as a result mutations are readily produced by irradiation of the sex cells. Ionizing radiation produces its effects by splitting chromosomes or activating the molecule of a gene in such a way that molecular rearrangement and change occurs. These changes may be permanent and mutations are formed.

One of the major issues frequently discussed with regard to the siting of nuclear power facilities focuses attention on the fact that an increase in the radiation of the environment might in turn result in an increase in the number of mutations which are occurring within the population. Radiation has its particular genetic hazard and the mutagenic effects of manmade sources of radiation when added to natural and uncontrolled background radiation will no doubt continue to be an issue.

The knowledge of the effect on mutation rates of these and other environmental factors, such as the effects of infectious agents, has stimulated research interest. Since chemicals actually cause mutations, it may be possible to determine the specific nature of the changes and, through the use of chemicals, induce a desired change in a gene, correct a deficiency, for example. The use of radiation in experimental work with animals and plants has already significantly broadened our knowledge of inheritance principles, and for example, has permitted the deliberate production of advantageous mutations in hybrid plants of agricultural significance.<sup>9</sup> Recognition of radiation and chemical effects on cell division processes, particularly with regard to the effect on mitosis, has resulted in increasing knowledge about better treatments for cancer.

<sup>7</sup> James F. Crow. *Chemical Risk To Future Generations*. *Scientist and Citizen*, vol. 10, June-July, 1968, pp. 113-117.

<sup>8</sup> L. Fishbein, et al. *Chemical mutagens: Environmental Effects On Biological Systems*. (Academic Press, New York, 1970). 364 p.

<sup>9</sup> Bjorn Sigurbjornsson. *Induced Mutations in Plants*. *Scientific American*. Vol. 224, January 1971, pp. 860-95.

### III. GENETIC ENGINEERING

#### *Introduction*

Progress in genetic engineering research can be considered as nothing more or less than a continuous and accelerating rate of refinement of a vast spectrum of biomedical knowledge. The history of medicine has been replete with similar progress. Many benefits have already been made available from the research in genetic engineering and the possibilities have only been sampled. The need is for a careful consideration of the implications of all the developments associated with genetic engineering so that the benefits versus the potential costs to society may be identified and with this knowledge control and regulation may be established as seems necessary and desirable.

The paragraphs which follow are intended to serve as an introduction to the various sciences and technologies which are associated in some way with the new developments in genetic engineering. The information is by no means complete, particularly with regard to current research, and the reader is encouraged to examine some of the selected references listed in the Appendix for more detail.

#### *Eugenics*

Eugenics is defined as:

- 1 The study and control of various possible influences as a means of improving the hereditary characteristics of a race.
- 2 Negative eugenics is that concerned with the prevention of the mating of individuals possessing inferior or undesirable traits.
- 3 Positive eugenics is that concerned with promotion of optimal mating of individuals possessing superior or desirable traits.<sup>1</sup>

While the utilization of the principles of eugenics has had notable success in animal husbandry and the plant sciences, there has been little extensive application on a voluntary basis in human populations. In fact, there has been considerable controversy about the use of eugenic principles for the improvement of mankind. As Dr. Lederberg has pointed out:

We are on the shakiest ground trying to sort out the genetic basis of such social diseases as crime and delinquency.<sup>2</sup>

Eugenics is now viewed by many modern proponents as the utilization of informed decision by individual couples to determine family size, the reduction of birth frequency of genetically determined diseases by a combination of genetic counseling and screening, and positive eugenics in the form of encouragement of parents with socially

<sup>1</sup> L. R. C. Agnew, et al., *op. cit.*, p. 519.

<sup>2</sup> Joshua Lederberg, *Experimental Genetics and Human Evolution*, *The American Naturalist*, vol. 100, September-October 1966, p. 525.

valuable qualities such as intelligence, energy, sensitivity, and mental stability. The need for negative medical eugenics is considered even more pressing today because of the increasing number of individuals within the population who have genetically induced diseases.<sup>3</sup>

Some of the events which might be increasing the incidence of these genetic diseases include the increase of ionizing radiation in the environment, the increased exposure to chemical mutagens, and possibly the effect of greater utilization of radiation for medical purposes. The improvement in medical care now results in more individuals reaching reproductive age who carry traits for defects which would have prevented survival in early times.

One recent controversial issue has been the debate surrounding the anomaly known as the XYY defect. In this defect, the male has an extra Y chromosome and studies have suggested that there might be a relationship between criminal behavior and the genetic abnormality. In a recent test case, an injunction against a study of this anomaly in an individual was sought on the basis that such a study would violate constitutional safeguards.<sup>4</sup> These studies are continuing in other places, however, and some investigators are developing information which supports a contention that XYY males are more prone to aggressive behavior. Further, the suggestion has been offered that this abnormality should be considered in evaluating responsibility in a court of law.<sup>5</sup> The association of chromosome abnormality with a sociopathic behavior has various ethical and medicolegal implications. One suggestion is that early prediction of behavior potential might be possible as more data are made available on the real significance of this abnormality. There is already concern that information about this defect might be used to influence decisions regarding infractions of the law, for example, during parole applications.

When the general field of behavioral genetics is examined in the context of eugenic principles, several extremely powerful issues emerge. For example, the field of education is now in a turmoil as a result of the controversial hereditary/intelligence issue. A committee of the National Academy of Sciences recently prepared a report which indicated the need for careful and extensive consideration of all aspects of behavioral genetics.<sup>6</sup> Again, Joshua Lederberg provided insight into the thinking of some geneticists with regard to these aspects of eugenics when he said:

Most geneticists would wait on a deeper knowledge of human genetics before considering statutory intrusion on personal liberties in this sphere.<sup>7</sup>

The development of techniques for freezing and storing sperm, the possibilities for external fertilization of eggs, the standardization of artificial insemination techniques, and, in general, all of the associated skills of genetic engineering could be combined with the principles of

<sup>3</sup> The New Eugenics, *The Lancet*, vol. II, Oct. 1971, pp. 751-752.

<sup>4</sup> Richard M. Cohen, Genetic Study Is Opposed, *the Washington Post*, Feb. 7, 1970, p. B2.

<sup>5</sup> Lytt I. Gardner and Richard L. Neu, Evidence Linking an Extra Y Chromosome to Sociopathic Behavior. *Archives of General Psychiatry*, vol. 26, March 1972, pp. 220-222. (For a more detailed discussion of this problem see: Report on the XYY Chromosome Abnormality, the National Institute of Mental Health, PHS Publication No. 2103, 1970, 55 pages.)

<sup>6</sup> Kingsley Davis, et al., Recommendations With Respect to the Behavioral and Social Aspects of Human Genetics, *Proceedings of the National Academy of Sciences*, vol. 169, Jan. 1972, pp. 1-3.

<sup>7</sup> Joshua Lederberg, *American Naturalist*, *op. cit.*, p. 530.

eugenics. However, there is a great deal of concern being expressed about the procedures by which criteria will be selected for the identification and classification of "desirable" traits to be favored and "undesirable" traits to be eliminated. Since such selections are, at best, made on the basis of subjective criteria, the application of principles of eugenics, particularly with regard to behavioral and social criteria, will continue to be a controversial topic warranting careful attention. Modern eugenicists have a much broader view of eugenics than older founders as illustrated by a recent comment:

Society's goals can best be served by efforts directed to the improvement of the environment on a broad scale, prenatally and postnatally, so that every genotype can realize its potential and optimize its phenotype. The problem deserving priority after "euthenics" (environmental improvement) is that of stabilizing the quantity of the population. Preservation of the status quo of the quality of the gene pool and the avoidance of deterioration can proceed concurrently for humanitarian reasons as can "euthenics"—improvement of the phenotype by biological means. Once the range of family sizes has been reduced to zero to three, an opportunity for selection will still exist that could be cautiously pursued by an enlightened society. Policy making should be guided by the goals of optimizing the quality of the gene pool and the diversity of phenotypes via an index of social value rather than the maximization of a few traits that myopically, seem ideal. The task ahead is awesome.<sup>8</sup>

#### *Euteleogenesis*

This term is defined as:

The artificial insemination by semen of a donor selected because of special characteristics for the production of superior offspring."<sup>9</sup>

Artificial insemination has been widely practiced in animal husbandry for a long time and procedures for collecting and storing sperm have become quite sophisticated. The advantages are obvious; the breeds have been improved through the selection for specific traits such as meat and milk production.

Artificial insemination techniques in human beings progressed rather slowly at first and then became more readily available under conditions rather carefully controlled by the physician. Artificial insemination in human beings has usually been limited to those instances where careful study has failed to indicate the specific cause of infertility or where infertility has definitely been attributed to the male. Two types of artificial insemination are practiced—AID, artificial insemination donor, where the donor is usually unknown to the parents, and artificial insemination husband (AIH). Under normal circumstances, the physician usually has provided careful counseling and the selection of a donor is usually based upon medical criteria such as similar physical characteristics, ethnic background, intelligence, etc. There are legal as well as moral difficulties associated with artificial insemination which require such steps as the signing of consent forms

<sup>8</sup> I. I. Gottesman and L. Erlenmeyer-Kimling. Prologue: A Foundation for Informed Eugenics. *Social Biology*, vol. 18, Supplement, September 1971, pp. S1-S8.

<sup>9</sup> L. R. C. Agnew, et al., *op. cit.*, p. 520.

to insure protection for the physician and to provide at least some semblance of legality for the child. In most instances, there are no laws which insure legitimacy to the child born as a result of artificial insemination.<sup>10</sup> The moral issues are even more complex and require careful thought on the part of the prospective parents. Artificial insemination also has been discussed with concern from the concept of eugenics since this is one technique which could be used to secure maximum utilization of an "optimal" mate.

The advent of the vasectomy as a birth control technique and the increasing acceptance of the technique in this time of public concern with the growth in population has produced a new commercial venture. A limited number of "sperm banks" are now available for the storage of human sperm. Since the vasectomy is generally considered to be an irreversible operation, the concept of preserving sperm prior to the operation for possible later use has been developed. (There have been some successful repairs of the severed ducts by surgical means.) The "bank" provides the facilities for the collection and low temperature storage of a sample of sperm. The individual can "withdraw" a stored sample for use later on.<sup>11</sup> The use of commercial sperm banks has been criticized on several points. First, although there has been some experience with frozen human sperm the American Public Health Association has expressed concern with the fact that there are insufficient data to warrant any conclusions at this time that long term (in years) storage of human sperm would maintain viability of the sperm. On the other hand, there has been some experience with frozen human sperm used successfully in artificial insemination. Dr. Samuel J. Behrman, University of Michigan, has reported 104 fully documented successful fertilizations with sperm stored for more than 16 months.<sup>12</sup> He points out that the use of older sperm has reportedly been successful; the problem is that adequate documentation of the use is not available to permit full evaluation to support the reports of successes.

Another major concern with regard to the establishment of commercial sperm banks, aside from the reactions to the absence of laws regulating the policies of the banks, has to do with the ethics of sperm banks as a concept. These ethical concerns center around the unregulated commercial exploitation of the vasectomy candidate and the ethics of using these unregulated banks as a commercial source of donor sperm for artificial insemination. The potential of fostering eugenics aims in an unregulated manner is included in this latter concern.

The technology for preparing the sperm for storage at low temperature is reasonably well developed. Some difficulty has been encountered in thawing the sperm to secure full motility but this does not seem to be a problem of real concern. Further improvements may permit the candidate parents to select the sex of their child. The long experience with animal artificial insemination has provided the equipment and the techniques; the concern with population growth has provided the need. Establishment of sperm banks and the commercialization of artificial insemination occurred without advance evaluation of the various social, legal, and ethical implications.

<sup>10</sup> Henry G. Lynch. *Dynamic Genetic Counseling for Clinicians* (Charles C. Thomas, Springfield, 1969), p. 269.

<sup>11</sup> Constance Holden. Sperm Banks Multiply as Vasectomies Gain Popularity. *Science*, vol. 187, Apr. 7, 1972, p. 32.

<sup>12</sup> Success with Frozen Sperm. *Medical World News*, Mar. 24, 1972, p. 44L.

While the technique of freezing sperm has been rather successful, particularly in veterinary medicine, storage of the egg has been more difficult. Recently, however, D. G. Whittingham at Cambridge reported his success with the low-temperature storage of fertilized eggs of the mouse. A high proportion of viable zygotes were obtained following removal from storage and some successful implantation and development of fetuses occurred.<sup>13</sup> Research workers at Oak Ridge National Laboratory have refined and improved the techniques for mass producing and deep freezing the embryos.<sup>14</sup> This technique has a number of potential applications including the possibility that in vitro fertilization combined with low-temperature storage might someday make it possible to store embryonic forms of various species for long periods with later removal from storage for development. The technique is in the earliest stages of development.

### *In vitro fertilization*

There has been a great deal of interest in developing the techniques for removing viable eggs from the human ovary, fertilizing these eggs in the laboratory (in vitro), and then returning the fertilized egg, at some early stage of development, to the uterus for the completion of development and normal delivery. Aside from the fundamental research interest in studying the very early stages of human development, several medical reasons support the development of in vitro fertilization in human beings. The primary justification offered is for the treatment of infertility of the female due, for example, to a block in the fallopian tubes which prevents normal conception. (Opponents of the technique insist that improved surgical intervention would in most instances correct this type of infertility.) Another more questionable justification is that sex determination could be accomplished if embryo transfer became feasible; some genetic diseases are sex-linked, and occur most frequently in the male, only females would be transferred when the genetic history indicates a high risk for males. Another justification, and admittedly more controversial, is that the more sophisticated engineering techniques, such as gene therapy, would be more effective during the early stages of development.<sup>15 16</sup>

The techniques for removing the eggs, securing fertilization in culture in the laboratory, and initiating the first few stages of cell division have been reasonably well worked out at this point.<sup>17</sup> In fact, this phase of the procedure has been so successful technically, that rumors have been in the news media for some time about the return of a human blastula (hollow ball stage of the embryo) to the uterus.

There is nothing particularly new about the concept of removing a fertilized egg from a mammal, and then returning the fertilized egg to a mammalian uterus (frequently a different animal of the same species) for final development. The technique has been known in animal

<sup>13</sup> Frozen Embryos, *The Lancet*, Oct. 9, 1971, pp. 806-807.

<sup>14</sup> Walter Sullivan. Frozen Mouse Embryos Grow In Foster Mothers. *New York Times*, Aug. 15, 1972.

<sup>15</sup> Robert G. Edwards and David J. Sharpe, Social Values and Research in Human Embryology. *Nature*, vol. 231, May 14, 1971, pp. 87-91.

<sup>16</sup> R. G. Edwards, P. C. Steptoe, and J. M. Purdy, Fertilization and Cleavage in Vitro of Preovulator Human Oocytes. *Nature*, vol. 227, Sept. 26, 1970, pp. 1307-1309.

<sup>17</sup> R. C. Edwards, and Ruth E. Fowler, Human Embryos in the Laboratory. *Scientific American*, vol. 223, December 1970, pp. 45X54.

husbandry for some time and has been completed successfully on many occasions in such farm animals as sheep, goats, and cattle.<sup>18</sup> The technique of in vitro fertilization has also been tested experimentally in laboratory animals such as rabbits, hamsters, and mice to the point of transfer to the uterus and full development in the case of mice with successful reproduction of the progeny of the implantation.<sup>19</sup>

The major criticism of this type of research in human beings is ethical, although social and legal values also are dominant in many discussions of the technique. Concern about the ethics of experimental development of human fetuses has been expressed on many occasions. As Leon Kass has summarized this problem:

One cannot ethically choose for a child the unknown hazards that he must face, and simultaneously choose to give him life in which to face them.<sup>20</sup>

He is joined by others in the concern about in vitro fertilization experiments on human beings. On the one hand some researchers are prepared to take the step of implanting the in vitro fertilized embryo and yet, in the opinion of the objectors, there are insufficient data about the risks involved. It is emphasized that every step of the manipulation introduces a special hazard up to and including the actual implantation in the uterus. This risk at worst might result in the production of a horribly malformed individual and at the least would probably, at this stage, not provide enough information to warrant assumption that the technique would be safe for general application. Only preliminary data are available on the use of this technique in nonhuman primates (the Macaque monkey, for example). Normal protocol in biomedical experimentation requires the evaluation of new techniques in a series of species including full evaluation in nonhuman primates for risky ventures.

Other experimental procedures are very closely associated with in vitro fertilization. The nature of science is to constantly project new hypotheses to be tested. In the case of in vitro experiments the hypothesis considers the necessity for returning the fertilized egg to the uterus for final development. Active growth and early development of the human zygote has been achieved in culture. What obstacles prevent retention and continued development under laboratory conditions? This question, along with the medical interest in providing for the maintenance and care of the prematurely born infant, has resulted in investigation of the processes of implantation in the uterus, development of the placental membranes, and other factors associated with in utero development. Research workers have probed along the lines of continuous culture of human cells of various types,<sup>21</sup> successful implantation of a mouse embryo on rattail collagen in a test tube,<sup>22</sup> fetal

<sup>18</sup> L. E. A. Rowson. Egg Transfer in Domestic Animals. *Nature*, vol. 233, Oct. 8, 1971, pp. 379-381.

<sup>19</sup> Anil B. Mukherjee and Mainmon M. Cohen. Development of Normal Mice by in Vitro Fertilization. *Nature*, vol. 228, Oct. 31, 1970, pp. 472-473.

<sup>20</sup> Leon R. Kass. Babies by Means of in Vitro Fertilization: Unethical Experiments on the Unborn? *The New England Journal of Medicine*, vol. 285, Nov. 18, 1971, pp. 1174-1179. (See also this recent paper by Kass in the appendix.)

<sup>21</sup> Philip Glade. Cultured Humanity. *New Scientist*, Jan. 6, 1972, pp. 30-31.

<sup>22</sup> An Embryo Implants in a Test Tube. *New Scientist and Science Journal*. Apr. 15, 1971, p. 137. (See also: Yu-Chin Hsu. Differentiation in Vitro of Mouse Embryos Beyond the Implantation Stage. *Nature*, vol. 239, (Sept. 22, 1972, pp. 200-202).

growth in culture,<sup>23</sup> and—preparing for investigation of the problems associated with the final stages of development—research on an artificial uterus.<sup>24</sup>

In this latter type of research, the researchers use placentas delivered during childbirth (separated at childbirth) to investigate the problems of fetal and maternal circulation. The immediate objective of this research is to try to gain an understanding of the problems in pregnancy so that miscarriages, abnormal fetal development, et cetera can be treated more successfully. In the total scope of in vitro fertilization, however, research on devices of this type are cited as the closing of the gap from ovulation to birth in a totally synthetic environment.

One of the difficulties in working with cells of vertebrate animals has been the fact that each trait is governed by at least two genes, one on each chromosome. In the case of recessive traits, the presence of an opposing dominant factor conceals the presence of any recessive gene. Geneticists have worked for years to develop a culture of cells with only one set of chromosomes per cell (haploid cells).<sup>25</sup> The haploid culture technique should serve to simplify, somewhat, many of the problems involved in experiments with diploid organisms.

Associated with this same research on haploid organisms and of interest in research on in vitro fertilization have been some advances in the stimulation of parthenogenesis (development of the egg without fertilization). Although this technique had been used with some success with rabbits (and with more success in non-mammalian species) for some time, there had been little success with the mouse, a more useful laboratory animal. Egg activation is of interest because the organism has the traits of only one parent, the female, thus simplifying genetic studies. In this technique, the egg is stimulated either electrically or chemically, and division is induced.<sup>26 27</sup> Some of the cell groups which develop contain only one-half a set of chromosomes (haploid), some cultures are a mixture of cells with haploid and diploid condition, and other cultures are diploid as though normal meiotic (reduction) division had not occurred or the chromosomes reached the double number in some way after reduction division. A considerable number of problems must be solved before any degree of successful development to a complete mammalian organism will occur following parthenogenesis. The technique does have a continuing usefulness from the standpoint of the study of haploid cell cultures. However, the major objection to in vitro experimentation in human beings still remains. This objection focuses attention upon the ethics of performing experiments upon the "unborn and the unconceived." This question contributed significantly to an editorial statement of the American Medical Association calling for a moratorium on in utero implantation of a human in vitro fertilized egg. Whether this plea will be heeded throughout the world remains to be seen.

<sup>23</sup> D. A. T. New and Merle Mizell. Opossum Fetuses Grown in Culture. *Science*, vol. 175, Feb. 5, 1972, pp. 533-536.

<sup>24</sup> Artificial Uterus Furthers Research on Live Placentas. *Medical Tribune*, Oct. 27, 1971, p. 29.

<sup>25</sup> Jerome J. Freed and Liselotte Mezger-Freed. Stable Haploid Culture Lines From Frog Embryos. *Proceedings of the National Academy of Sciences*, vol. 65, February 1970, pp. 337-344.

<sup>26</sup> C. F. Graham. Parthenogenetic Mouse Blastocysts *Nature*, vol. 226, Apr. 11, 1970, pp. 165-167.

<sup>27</sup> Andrezeg K. Tarkowski, et al. Experimental Parthenogenesis in the Mouse. *Nature*, vol. 226, Apr. 11, 1970, pp. 162-165.

### *Clonal Propagation*

The term "clone" is now being used to refer to the tissue culture, or asexual reproduction of cell colonies. The term has been defined as "a strain of cells descended in culture from a single cell."<sup>28</sup> The initial impetus to an expanded research program on cloning techniques came from investigations of the tissue culture of plant cells. It is possible to grow asexually new plants, such as carrots, from vegetative cells or cuttings taken from a mature plant or another culture. The procedure also now is used for maintaining tissue cultures of human cells in many research laboratories. There has been sufficient work completed in the past decade to demonstrate that it is possible to culture almost any cell in a liquid culture medium. This type of culture has been particularly significant in the study of growth patterns of abnormal cells such as those which occur in cancer. In fact, cells taken from cancer patients have been maintained in culture for some time. Tissue cultures of cells from human beings with inherited diseases are being studied to identify chromosome defects associated with the disease. Samples of human fetal tissue can be cultured and certain diseases diagnosed prior to birth. This latter technique, known as amniocentesis, is discussed in more detail under the topic of genetic counseling. Human cell cultures are being used for making vaccines and for studying virus infection processes. As discussed in the preceding section, the stimulation of the egg by artificial means provides an opportunity to culture cells with only one set of chromosomes.

More recently, cloning has been associated in the mind of the layman, and in scientific articles as well, with the possibility of "fabricating man" or producing large numbers of identical individuals by tissue culture techniques. This concept follows in the path of an interesting variation of *in vitro* fertilization techniques with which some success has been achieved with some vertebrate animals (frogs and toads, for example). The egg is manipulated so as to destroy the nucleus containing the female set of chromosomes. Another nucleus with a diploid set (the normal set of chromosomes in a body cell) taken perhaps from a cell lining the intestines of the same individual, is then inserted into the egg, and the egg, stimulated as though it had been fertilized in a normal fashion, then begins to grow and develop into an organism—identical in all respects to the source which furnished the diploid number of chromosomes. Any body cell, either from the male or the female, could serve as the source of the diploid set of chromosomes and the progeny would be identical in all respects with the parent which furnished the set of chromosomes. In the case of human beings or other mammals it would not even be necessary to return the egg to the same female which furnished the egg originally. The sophisticated research being conducted in animal breeding has shown that eggs from one female may be implanted in the uterus of another female with a high degree of success.

If this technique is considered in the light of many of the other developments in genetics and embryology, cloning is then visualized as a system of (1) removing an egg, (2) substituting the desired nucleus (perhaps large numbers of eggs and nuclei, thus producing

<sup>28</sup> L. R. C. Agnew et al., *op. cit.*, p. 315.

large numbers of individuals with exactly the same characteristics), (3) culturing the new individuals in artificial uteri, (4) and then "harvesting" the new crop of identical human beings. A further step is the possibility of total synthesis of cells with the exact gene composition and then carry out the culture of "planned" individuals.

This type of "fabrication" in human beings is not now possible. While the substitution of a diploid nucleus for the haploid nucleus of the eggs has been achieved in amphibians (the frog, for example), application of the technique has not been extended to mammals. However, the human egg has been fertilized in the laboratory and the issue of implanting the fertilized egg back into the uterus for development is very real at this time. The use of a totally synthetic environment for rearing a mammal from the fertilized egg to development, while under investigation, is far from an accomplished fact. Nevertheless, all phases of the development, including the problem of gene activation within the transplanted nucleus, are under some sort of investigation. The synthesis of all these developments is a very real potential. Thus, the technique of "cloning" might be considered an advanced type of genetic engineering although no change in the composition of the genes on the chromosomes will probably be involved in the first efforts. In the long run, this technique might be further refined to permit the introduction of DNA, wholly synthesized in accordance with some set of specific criteria, and thereby achieve some ultimate objective in genetic engineering.

#### *Medical Genetics and Genetic Counseling*

The study of the inheritance of metabolic diseases and physical defects is beginning to produce beneficial returns at a rapidly accelerating rate. Many inherited diseases, so-called "inborn errors of metabolism," can now be treated very effectively. As a result, individuals with such defective genes are surviving in increasing numbers to reproductive age and there has been some conjecture that there may be a gradual increase in the incidence of inherited diseases. The number of diseases identified has been increasing as the analytical skills of the cytogeneticist have improved.

The medical geneticist deals with more than disease factors. The specificity of blood transfusion techniques and the progress which has been made in organ transplantation have all been made possible because of the knowledge available on the inheritance of blood types and other immunological factors. The proposals for the establishment of "tissue typing centers," analogous to the blood distribution centers, to facilitate the matching of organ donors with recipients are based upon the contributions of the field of medical genetics to the study of immunological reactions.

Treatment of the many metabolic diseases has evolved as the biochemical effects of the genetic defect have been described. These treatments may include the use of special diets to supplement or negate, as appropriate, the effects of the metabolic deficiencies involved; the avoidance of drugs rendered ineffective or dangerous because of genetic disorders; adjustment of enzyme concentrations to compensate for genetic deficiencies; or organ transplant or other surgical therapy.

Genetic counseling is intended "to disseminate understanding and knowledge concerning genetic problems as they arise."<sup>29</sup> Genetic counselors use family histories, new techniques in chromosome analysis, evidence from population genetics, and new concepts of the inheritance of various disorders. Clinics are being established for the purpose of providing advice to patients on genetic problems—usually in relationship to prospective parents and their concern with the possibilities of transmitting defects. Genetic counselors also aid in the diagnosis of pathogenic factors and in this way can define inherited defects so as to facilitate treatment. "Genetic counseling is 'eugenic,' a term coined by Galton, and covers aspects for the improvement of the human race."<sup>30</sup> Through genetic counseling, individuals with a history suggesting that undesirable genes might be transmitted can make their choices in childbearing on the basis of full and reliable information on probabilities of inheriting defects and consider the available alternatives.

Some prenatal genetic diagnosis is now possible and the availability of information on the developing fetus has strengthened the field of genetic counseling. Amniocentesis, a technique for the withdrawal of fluid from the amniotic cavity, is the principal means for studying genetic disorders of the developing embryo. The fluid surrounding the fetus within the uterine cavity contains excretions and secretions from the fetus as well as exfoliated cells which can be cultured within the laboratory. The insertion of a needle into the amniotic cavity and the withdrawal of a small quantity of fluid permits the biochemical examination of the fluid and the culture and examination of fetal cells. The data which can be gathered are useful in confirming or negating the presence of genetic disease or for monitoring the life functions of a fetus developing at risk as a result of maternal deficiencies (as in Rh blood factor). In some instances, Caesarian section permits early removal and survival of a fetus in danger. In other instances, the data which are made available may lead to a recommendation for early abortion. Prenatal care has been improved significantly as a result of amniocentesis, combined with the use of ultrasound and X-ray for monitoring development. The success of amniocentesis as a technique for predicting the presence of genetic disease has been impressive. In the case of Tay-Sachs disease for example (an inherited metabolic disease), the accuracy of prenatal prediction has been exceptional.<sup>31</sup> Amniocentesis has been extremely useful in the management of Rh disease (an inherited blood disease) and for the confirmation of chromosomal abnormalities (Down's, Turner's and Klinefelter's syndromes as well as other chromosomal abnormalities). More than 44 hereditary metabolic disorders have already been detected prenatally or are considered potentially possible of detection. The determination of the sex of the fetus also is a fairly routine task.<sup>32</sup> The availability

<sup>29</sup> Erwin G. Rerrick. Genetic Counseling, The Journal of the Maine Medical Association. February 19, 1968, p. 33.

<sup>30</sup> Erwin G. Rerrick, *op. cit.*, p. 33.

<sup>31</sup> John S. O'Brien, et al. Tay-Sachs Disease: Prenatal Diagnosis. Science. April 2, 1971.

<sup>32</sup> Aubrey Milunsky, et al. Prenatal Genetic Diagnosis, New England Journal of Medicine, vol. 283, December 17, 1970, pp. 1370-1381; December 24, 1970, pp. 1441-1447; and December 31, 1970, pp. 1498-1503. These references also provide comprehensive bibliographies on this subject.

of amniocentesis has proved to be extremely useful as a supplement to the genetic counselor since many genetic diseases can now be detected in utero and a definite consideration of risks rather than estimates can now frequently be provided to the parents.

Some risks are associated with amniocentesis and for this reason the procedure is generally limited to those instances in which familial history indicates the possibility of a genetic problem. Two kinds of complications can generally occur when the procedure is utilized; those to the mother, and those to the fetus<sup>33</sup>:

Maternal:

- (1) The possibility of introducing infection
- (2) The danger of damaging a major blood vessel and causing hemorrhage
- (3) The potential danger of sensitizing the fetus to Rh factor (a blood disorder)
- (4) Possibly inducing abortion as a result of the procedure

Fetus:

- (1) Possible direct injury to the fetus
- (2) Possible induction of malformation in the fetus
- (3) Error in diagnosis due to twinning or other multiple fetuses
- (4) Mistakes in diagnosis due to overgrowth of maternal cells

The chance of any of these complications occurring at the hands of experienced specialists is considered slight with the incidence of serious complications estimated to be less than 1 percent. With the availability of new techniques for locating the precise position of the fetus, the chance of fetal damage is further reduced.

While genetic counseling and the skills of the medical geneticist are not currently available to all the general public, there have been a few applications on a national scale. Phenylketonuria (PKU) was the first genetic disease for which mandatory (by law) mass screening was initiated. In this disease, a biochemical abnormality, the lack of a gene to produce the enzyme phenylalanine hydroxylase, results in an accumulation of phenylalanine. When this amino acid accumulates, a toxic condition is produced which seems to contribute to, or be associated in some way with, mental retardation. Although the disease is still not curable, the early use of a diet low in phenylalanine may be beneficial. The development of a simple assay for testing for the presence of the PKU associated deficiency and the recognition of the beneficial effects of a controlled diet soon led to almost universal testing of all newborn infants in the United States.

The use of mass screening techniques for the detection of PKU seemed initially to be a program for which there would be no criticism. Today, however, this testing program is being subjected to a cost/benefit analysis which may result in some reduction of national screening. Although the costs of maintaining for life a PKU mentally retarded individual are high (estimates are \$200,000-\$250,000 per case), some communities with a very low incidence of PKU are assuming the risks of these costs and are canceling the requirements for

<sup>33</sup> Ronald G. Davidson and Mario C. Rattazzi. Prenatal Diagnosis of Genetic Disorders: Trials and Tribulations—Clinical Chemistry, vol. 18, February 1972, pp. 179-187.

mandatory testing in order to make the funds available for higher priority programs. In Washington, D.C., for example, no PKU infants were detected in 3 consecutive years of testing and the PKU test was dropped as mandatory.<sup>34</sup> In this instance, mass screening programs to detect another genetic defect in newborns and in adults has been adopted. In Washington, D.C., sickle cell anemia was determined to be a much more significant disease than PKU. In the case of sickle cell anemia, however, a different approach to the problem has to be taken. This disease, the trait for which is carried by about 10 percent of the American black population, has the highest frequency of all nonsex chromosome linked recessive disorders in this country. About one in 400 black children will inherit the trait from each parent and develop the disease. Only recently has any major federally supported effort been mounted to provide genetic counseling services to American blacks and to set up voluntary community screening programs for the adults and children in order to detect the carriers of the trait. Prenatal screening programs for this disease are not yet possible.

There are many problems to be solved, in addition to the setting of priorities by some technique such as cost/benefit analyses. As summarized by the genetics counseling and engineering group of the Hastings Center, these problems include:

1. Who should initiate a screening program?
2. What should be the criteria for defects to be screened?
3. To what extent—if ever—should screening be confined to ethnic groups sharing a “common” (sic) gene pool? Should it be voluntary or compulsory?
4. How will the screening be done? Will it necessarily entail abortion?
5. How should the objectives of a screening program be determined? In what way should general policies be set about the relative value of long-range changes in gene frequency versus the immediate amelioration of familial problems?<sup>35</sup>

If these problems are solved, the Hasting Center group believes another series of questions need to be posed:

1. Who will have access to the information?
2. What controls should be placed on its dissemination or use?
3. Do the persons screened have the right to know all of the data?
4. What moral, social, medical, and legal obligations do we accept when we screen populations?<sup>36</sup>

An additional concern which is being voiced about the expanding use of mass screening for genetic defects involves the risk to the individual being screened. These tests are considered by many investigators to be a potential source of psychological and social risk to the individual. The possibility exists that identifying an individual as a carrier of a genetic defect may result in some sort of social stigma which may in turn seriously affect the individual's life within the

<sup>34</sup> After Ten Years of PKU Tests, a Reevaluation, *Medical World News*, Nov. 19, 1971, pp. 43-44.

<sup>35</sup> Program in the Ethical Social and Legal Issues of Genetic Counseling and Genetic Engineering, The Hastings Center, Institute of Society, Ethics, and the Life Sciences, Institute Program Series No. 5, p. 4.

<sup>36</sup> Hastings Center, *ibid*, p. 5.

community. Unless adequate preeducation and posteducation are provided along with the results of screening, it has also been hypothesized that psychological damage may occur with serious consequences.

Since the scope of human experimentation is limited by social constraints, most of the genetic data on human beings have been collected from population studies combined with careful examination and evaluation of the chromosomes of individuals with known diseases. Successful treatments are not available for most of the serious inherited diseases but research is continuing and at least this aspect of genetic engineering (genetic counseling) seems to have immediate and reasonably acceptable applications.

### *Molecular Genetics*

A major emphasis in molecular biology is to determine the sequence of the DNA or RNA bases coding the activity of a particular gene and, ultimately, to determine the sequence and function of all the genes on all the chromosomes. When the sequence and chemical structure of the genes has been determined, the next step, already taken with some simple DNA, is to synthesize the genes. Recently, a team of investigators was successful in isolating a sequence of genes that control a particular function in a bacterium. This technical feat was hailed as a significant step toward gaining an understanding of the biochemical controls that genes exercise in regulating cell metabolism. Since a viral DNA has been synthesized, techniques now are available to begin work on the synthesis of other and more complex forms of DNA.<sup>37</sup> As the coding sequence of the DNA of higher organisms is deciphered, as it surely will be, more complex DNA will be synthesized to duplicate or modify natural forms of DNA. The opportunity then will be available, possibly even for application to man, to substitute the synthesized DNA for the natural DNA in the egg, sperm, or body cell and thus regulate the development of the individual.

An additional advantage which accrues once the structure of a gene is known is the ability to detect the precise point at which the change has occurred which in turn is producing the genetic deficiency of medical concern. This so-called mapping of the sequence of bases of a gene controlling a particular biochemical defect is an essential part of any step toward the ultimate corrective action. H. Vasken Aposhian visualizes the utilization of a corrected gene—whether a natural DNA which has been corrected or the utilization of a synthetic DNA with the correct gene, as a type of drug therapy. In this concept he considers the use of gene therapy as simply a much more sophisticated medical treatment involving the use of specific DNA to correct a defect just as other drugs are used for medical purposes today.<sup>38</sup>

Several methods are being examined for the controlled change of genes. For example, it is known that mutations occur in nature. The direct induction of mutations with chemicals (such as mustard gas) or ionizing radiation is possible. In the case of plant genetics where radiation has been used, the undesirable mutants are simply selected out and discarded. Directed mutation is continued until the desired

<sup>37</sup> W. Min Jou, et al., Nucleotide Sequence of the Gene Coding for the Bacteriophage M52 Coat Protein, *Nature*, vol. 237, May 12, 1972, pp. 82-88.

<sup>38</sup> H. Vasken Aposhian, The Use of DNA for Gene Therapy—The Need, Experimental Approach and Implications, *Perspectives in Biology and Medicine*, vol. 14, autumn 1970, pp. 98-108.

phenotype is obtained. Such a selection procedure could not be tolerated in human genetics. In fact, the possible inadvertent increase in mutations induced by radiation is of concern in the deliberations over the increased use of atomic energy for the production of power.

If a total or partial synthesis of a gene or group of genes is selected as a genetic engineering technique, then the new gene must be injected in some way into the cell or tissue. One possibility would be to add the synthesized gene into the somatic—body—tissue by injection and then hope that some of the new gene material would be incorporated. In the case of metabolic deficiencies, it is hypothesized that a corrective gene could be introduced into the tissue of the defective organ or gland where it would change the pathways of metabolic synthesis and correct the deficiency. This type of process, called transformation, has been accomplished with microorganisms and to a lesser extent with some animals. For a number of reasons, transformation is not considered to be readily feasible in man. As pointed out by Aposhian, "the blood serum of most animals contains highly active enzymes that hydrolyze (decompose) DNA."<sup>39</sup> Other techniques than direct injection are of greater current interest.

A technique which is considered to be a more exciting possibility, referred to as transduction, would permit the introduction of genes into the cell by means of a carrier virus. In this procedure, the desired genes would be incorporated within a nonpathogenic virus; the host would be infected with the virus; and through cell infection by the virus, the new genes would be introduced into the cell. In this way, the DNA would be injected by the virus directly into the cell without being exposed to the digestive enzymes of the circulatory system of the host animal. This concept of gene transfer has been attempted in a highly controversial experiment in West Germany which involved the infection of two young girls with a virus in an attempt to transfer a gene for correction of a serious enzyme deficiency which was producing mental retardation.<sup>40</sup> This type of research is continuing.

Of additional interest is the recent research report on the successful transfer into human cells in culture of a bacterial gene by means of a virus.<sup>41</sup> In this research, a culture of human cells with a gene deficiency was infected with a virus carrying the absent gene. After infection, the human cells exhibited the new enzyme activity, suggesting that effective gene transfer had occurred. Merrill's research is of great interest because it supports the concept that genes might be introduced into human cells using a virus as a carrier. The research, while very exciting to molecular biologists, requires further investigation and evaluation.

Merrill has pointed out that one of the great concerns with the technique of transduction is the fact that no one really knows anything about its side effects. As some of the effects might not be observable for many years, the use of the virus technique in large populations might

<sup>39</sup> Ibid., p. 102.

<sup>40</sup> James J. Nagle, Genetic Engineering, Bulletin of the Atomic Scientists, Dec. 1971, p. 44. (See also the paper by Friedmann and Roblin in Appendix 3 and the discussions by Newfeld, Sweeley, Rogers and Friedmann in Science, vol. 178, November 10, 1972, pp. 648-649.)

<sup>41</sup> Carl R. Merrill, et al., Bacterial Virus Gene Expression in Human Cells, Nature, vol. 233, Oct. 8, 1971, pp. 398-400.

be catastrophic if an undesirable long-term effect of routine therapy was concealed.

Transduction still requires a great deal more investigation before it can be accepted as a safe and reliable therapy. However, there is precedent for the use of this technique from the experiences gained thus far from viral vaccines and knowledge of the disease effects of virus infections.

A method which on first examination appears to be quite bizarre is the technique of cell fusion. Although the mechanisms are poorly understood, several experiments have shown that when selected cells from two different species are fused or merged in cell cultures, the chromosomes of one species will disintegrate but on occasion genes from the one species will be taken up by the cells of the other species and an effective gene transfer occurs. For example, M. Hill and Jana Hillova found that mouse DNA was incorporated into the DNA of cultured chicken cells.<sup>42</sup> In another experiment, chick DNA was incorporated into mouse cells.<sup>43</sup> In a similar type of cell fusion experiment, but of greater significance to man, hybrids of mouse and human cells indicated the retention of human DNA in the mouse hybrid cells.<sup>44</sup> More recently, a hybrid variety of tobacco plant was produced and grown to maturity through the use of the cell fusion technique. This event has been hailed as a significant breakthrough in genetic engineering.<sup>45</sup> The long-range significance of this method of gene transfer has yet to be established, although transferring or introducing a gene into a human cell by cloning and cell fusion techniques is being investigated as a distinct possibility.

Significant obstacles stand in the way of general adoption of any of these techniques of gene therapy. For example, very little is known at this time about the precise structure of any human chromosome; almost all detailed work has been completed only with bacteria and with viruses which infect bacteria—bacteriophages. On the other hand, information is being made available with regard to viruses which seem to be nonpathogenic for man and which could possibly be utilized for the transfer of genes. A particularly difficult problem is the fact that still less is known about the interaction of genes. Considerable progress is being made and emphasis by the molecular biologists is still being placed on the solution of all of these problems.

### *Euthenics*

Euthenics is defined as "the science of race improvement through the regulation of environment."<sup>46</sup> Scientific developments related to euthenics are often overlooked as a factor when discussions are held about progress in genetics. Arguments are continuous about the interactions of genetic potential and environment. Any casual observation of the current controversies in the entire field of educational reform

<sup>42</sup> M. Hill and Jana Hillova, Recombinational Events Between Exogenous Mouse DNA and Newly Synthesized DNA Strands of Chicken Cells in Culture, *Nature, New Biology*, vol. 231, June 30, 1971, pp. 261-265.

<sup>43</sup> A. G. Schwartz, et al., Correction of a Genetic Defect in a Mammalian Cell, *Nature, New Biology*, vol. 230, Mar. 3, 1971, pp. 5-8.

<sup>44</sup> Toshihisa Kusano, et al., A New Reduced Human-Mouse Somatic Cell Hybrid Containing the Human Gene for Adenine Phosphoribosyltransferase, *Proceedings of the National Academy of Sciences*, vol. 68, Jan. 1971, pp. 82-86.

<sup>45</sup> Peter S. Carlson, et al., Parasexual Interspecific Plant Hybridization, *Proceedings of the National Academy of Sciences*, vol. 69, Aug. 1972, pp. 2292-2294.

<sup>46</sup> L. R. C. Agnew, et al., op. cit., p. 520.

will suffice to emphasize this point. The inheritance of intellect is under examination as well as the entire sphere of behavioral control as influenced by inherited and environmental factors. Experiments with deaf children, for example, have shown that the teaching techniques may be at fault rather than the inherited intellectual ability of the child limiting the degree of achievement. Imagine the lot of Helen Keller if she had not had a devoted and talented teacher.

If an attempt is made to select desirable genetic criteria for propagation there must be a high degree of assurance that the characteristics observed are primarily controlled or influenced by the gene and not by superimposed environmental effects. Separation of the limits imposed by inheritance from those imposed by environment is difficult in such areas as intelligence and the development of attitudes.

Investigations of the effect of nutrition on intelligence during the early development of children suggest that a nutritionally deficient environment retards both intellectual and physical development. Mutagenic chemicals and radiation exposure produce poorly understood genetic effects. These latter factors contribute a significant and detrimental effect by increasing the rate and incidence of undesirable mutations. No amount of genetic counseling can modify the adverse effect of this type of environment. Only stricter control of the undesirable environmental factors can alter the adverse effects although abortion can be recommended where monitoring indicates a defective fetus.

Some mutations are difficult to classify as to desirability. A particular mutation may be an advantage in one environment and a disadvantage in another. An example of this type of environmental adaptation is seen with sickle cell disease, a blood disorder found in some Negroes. This disease has serious consequences but is believed also to provide some resistance to malaria. Where malaria is not common, the serious consequences of the disease far outweigh any protective advantage. Mutations are a mechanism of adaptation and the complete elimination of genetic change, if ever possible, might result in a reduced chance of survival of a species in a changing environment. In fact, some species are believed to have become extinct as a result of an inability to adapt rapidly.

New knowledge in fetology, the study of the development of the fetus and embryo before birth, suggests that the environment of the child at this early stage of development may have a significant influence on total development.<sup>47</sup> The effects of thalidomide on the fetus could easily have been misinterpreted at one time as being due to genetic factors. The problem of distinguishing environmental from genetic influences must be solved before eugenics practices can be extended.

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<sup>47</sup> A. Werch and R. H. Kaufman. Fetal Monitoring. *American Family Physician*, April 1972, pp. 91-97.

#### IV. SOCIETAL CONCERN ABOUT GENETIC ENGINEERING

##### *Technological Impact*

The history of mankind is replete with examples of technological innovation. The discovery and utilization of fire; the invention of clothing to provide protection against the elements; the ability to mine and refine metals; the advancements in the use of synthetic materials; and the other obvious technological achievements of modern society are abundant evidence of man's inventive exploitation of his environment. At the same time, curiosity about the nature and origin of life has led to significant developments in plant and animal breeding and in medicine. The discovery of the sperm and egg and the relationships which these cells play in evolution and reproduction rank among the most significant achievements in biology. This discovery, together with the refinement of knowledge about evolution and selection processes, has been followed by an increasingly sophisticated understanding of (and the capability to modify) the various events associated with human reproduction. In the absence of viable sperm, sperm can be provided by a donor; when the egg does not follow the natural course of development, ovulation can be stimulated and assisted. If fertilization does not occur internally (in vivo) external fertilization (in vitro) is now feasible, and artificial implantation may soon follow.

Advances in chemistry and physics have been matched by advances in biochemistry and biophysics. Refinements in these sciences have supported in turn advances in medicine and biology. Achievements in molecular biology and genetics are now adding new dimensions to the quest for knowledge of life and a renewal of concern about this quest. Old objections to further research are being revived and new objections are being raised.

Many writers have been warning for the past decade that the life scientists are on the verge of a revolution in biology. Robert Sinsheimer, of the California Institute of Technology, provided his estimate of the significance of these developments when he said:

I think this possibility of making deliberate genetic changes in man is potentially one of the most important concepts to arise in the history of the race. I can think of none with greater long-range implications for the future of our species. Indeed, this concept marks a turning point in the whole evolution of life. Even in the ancient myths man was constrained by his essence. He could not rise above his destiny. This day we can envision that change and choice.<sup>1</sup>

<sup>1</sup> Robert L. Sinsheimer. Genetic Engineering: The Modification of Man. Impact of Science on Society, vol. XX, No. 4, 1970, p. 280.

Dr. James J. Nagle, Department of Zoology, Drew University, in a recent review article said:

Modern genetics is on the verge of some truly fantastic ways of "improving" the human race, but let me emphasize at the onset that this technical know-how does not automatically bring with it the criteria for its use. This, I believe, is the most important fact that scientists and citizens alike must keep in mind as our technology progresses. It may be true that man has tremendous genetic potential for significant improvement, but in what direction? <sup>2</sup>

On a note of moderation and in a call for careful consideration, Bernard D. Davis, Harvard Medical School, wrote:

While such dangers [fear of tampering with man's inner nature] clearly exist, it also seems clear that some scientists have dramatized them in order to help persuade the public of the need for radical changes in our form of government. But however laudable the desire to improve our social structure, and however urgent the need to improve our protections against harmful uses of science and technology, exaggeration of the dangers from genetics will inevitably contribute to an already distorted public view, which increasingly blames science for our problems and ignores its contributions to our welfare. Indeed, irresponsible hyperbole on the genetic issue has already influenced the funding of research. <sup>3</sup>

In a statement which goes beyond narrow consideration of the technological feasibility of genetic engineering, Herman Kahn voices the concern heard most frequently in forums on the moral aspects of these developments:

For many of us, though, there are great emotional and value objections to artificial human reproduction in the laboratory or choosing our children's characteristics like flower-seed packages. Is it really necessary to breed embryos in the laboratory in order to learn how to correct defective genes? Even if feasible, will we want to go beyond the "negative" eugenics of preventing defects from being passed on, and manipulating genes to reduce disease? Will we move beyond into the "positive" eugenics of improving what are considered today to be average human characteristics? If a great upcoming social problem in biochemical brain research is "who is to control the mind-controllers?" a similar problem will arise in genetics research: Who is to control the genetic engineer and according to what values? <sup>4</sup>

The Nation has progressed through a series of relatively minor crises in medical technology. Minor, that is, in terms of comparison with these developments hypothesized as being on the verge of breakthrough. Who would have estimated that chemical control of the conception process would ever have received such widespread acceptance

<sup>2</sup> James J. Nagle, *op. cit.*, p. 44.

<sup>3</sup> Bernard D. Davis. Prospects for Genetic Intervention in Man. *Science*, vol. 170, December 18, 1970, p. 1279.

<sup>4</sup> Herman Kahn and Anthony J. Wiener. *The Year 2000*. (London, The MacMillan Co., 1967), p. 113.

in such a short period of time or that the collapse of barriers to abortions on demand would have appeared so rapidly? Equally dramatic changes in attitude have accompanied the rapidly evolving capabilities to provide life sustaining support in the form of kidney machines, heart-lung devices, and the use of nuclear pacemakers and heart pumps. Although the turmoil concerning the first heart transplant has subsided somewhat, ethical issues remain unsolved. The issue of human experimentation has been revived recently by the reports of experimental whole body irradiation of terminal cancer patients and the long term study of syphilis.<sup>5 6</sup> These developments, while significant examples, are considered by many investigators to be milestones in medical research and technical capabilities in the new understanding of life processes associated with developments in genetics engineering.

Leon R. Kass expressed the concern being felt about the developing technology of genetic engineering in a recent paper:

We have paid some high prices for the technological conquest of nature, but none perhaps so high as the intellectual and spiritual costs of seeing nature as mere material for our manipulation, exploitation and transformation. With the powers for biological engineering now gathering, there will be splendid new opportunities for a similar degradation of our view of man. Indeed, we are already witnessing the erosion of our idea of man as something splendid or divine, as a creature with freedom and dignity. And clearly, if we come to see ourselves as meat, then meat we shall become. The new technologies for human engineering may well be the "transition to a wholly new path of evolution." They may therefore, mark the end of *human* life as we and all other humans know it. It is possible that the non-human life that may take our place will in some sense be superior—though I personally think it most unlikely, and certainly not demonstrable. In either case, we are ourselves human beings; therefore, it is proper for us to have a proprietary interest in our survival, and in our survival as *human beings*. This is a difficult enough task without having to confront the prospect of a utopian, constant remaking of our biological nature with all-powerful means but with no end in view.<sup>7</sup>

Joshua Lederberg, Nobel laureate and a professor of genetics at Stanford University School of Medicine, was one of the first to direct attention to the rapid pace of new developments in genetics, and especially to the technique of cloning. Although Dr. Lederberg has indicated that he does not believe that developments in genetics engineering should be considered lightly, he has expressed the view that the danger is not as great as has been envisioned by others. For example, when Nobel laureate James Watson chose to highlight his concern about cloning and genetic engineering by making these topics the theme of his address to the House of Representatives Committee on

<sup>5</sup> Body Radiation Program. Congressional Record—Senate. January 19, 1972, pp. 540-546.

<sup>6</sup> Forty Years of Federal Experiments on Victims of Syphilis. Congressional Record—Senate. July 26, 1972, pp. S11854-S11855.

<sup>7</sup> Leon R. Kass. Making Bables—the New Biology and the "Old" Morality. The Public Interest. Winter, 1972, pp. 53-54.

Science and Astronautics Symposium in 1971,<sup>8</sup> Dr. Lederberg commented on Watson's statement by noting:

There are indeed tigers within our walls that deserve more immediate attention [than experiments in human embryology] from our lawmakers. We can prevent moral dilemmas about how to remove genetic defects by paying more attention to preventive environmental hygiene. A scandalously small number of the additives we pour into our milieu—in drugs, foods, water, and air pollutants—have been tested for their genetic impact; and we have a long way to go in perfecting and reliably interpreting such tests. And to think that teachers and engineers are out of work when we still provide so stingily and so clumsily for the most important of gene products—the eager minds of the Nation's children!<sup>9</sup>

The end objectives of the research and new technologies in genetics have not been generally specified as the "fabrication of man." As with so many other technologies, small increments of genetic knowledge, when added together, suddenly provide an opportunity to accomplish major innovations. Advocates of the various fundamental life science programs emphasize the medical objectives to be achieved and the applications of these benefits for the alleviation of suffering. These objectives include:

- ①—diagnosis and treatment of infertility
- ②—identification and treatment of inherited disease
- ③—prevention of inherited diseases
  - improvement of genetic counseling techniques
  - provision for the care of the prematurely born infant
  - support of new techniques in fetology (care of the fetus)
  - expansion of fundamental knowledge about embryonic development
- ④—improvement of techniques of birth control (population control)
- ⑤—solution of immunological problems associated with rejection of an organ transplant
  - control of embryonic development and *in-vitro* fetal development with artificial placenta (care of the prematurely born infant)
- ⑥—improvement of abortion technique and prevention of undesirable abortion processes
  - improvement of prenatal diagnostic techniques
- ⑦—solution of the genetic code in human beings, including the mapping of gene position of chromosomes
  - determination of the genetically controlled differentiation process in development
  - acquisition of more fundamental knowledge of the effects of various mutagenic and environmental factors

<sup>8</sup> Panel on Science and Technology. Twelfth Meeting. International Science Policy. Proceedings before the Committee on Science and Astronautics. U.S. House of Representatives. 92d Cong., 1st sess. January 26, 27, and 28, 1971, pp. 336–366.

<sup>9</sup> Joshua Lederberg. Egg Transplants: Not the End of the World. The Washington Post, June 20, 1971, p. B2.

While all of the preceding applications can usually be justified as relevant in terms of health problems generally, there is still concern about the ultimate impact of these developments should routine utilization become possible. When the techniques for fertilization in the laboratory and genetic intervention can be combined with an effective artificial placenta, the potential for genetic engineering will have been achieved. There is concern that sufficient consideration is not being given to the impact of this potential sufficiently far in advance of achievement to prepare for wise decisions on the courses of action which should be taken. Those who are concerned state that:

- ① —it is possible that the changes produced by the use of genetic engineering techniques might force us to lead new and undesirable ways of life and to view life and the nature of man in an entirely different (and not necessarily better) light
- ② —improvements in alternative methods of treatment (surgery and positive eugenic methods) would provide less controversial methods of treatment and without the dangers associated with genetic intervention
  - risks from in-vitro processes are not sufficiently well known to avoid the production of gross deformities
  - moral and legal questions about the disposition of defective experimental embryos are of serious concern
  - the ethics of experimental work with fetuses and for informed consent of adults have never been resolved
  - social and political reaction is strong concerning the potential for misuse and abuse of powers to control human development
  - philosophic concern has not been resolved about the possible dehumanization of the nature of man and the social consequences of these changes

The concerns listed, and others as well, are being expressed with an increasing frequency by religious and lay persons, and by an increasingly vocal portion of the highly respected scientific community. As with other technological developments, it is possible that the development and use of these new techniques may be so far ahead of medical, legal and social controls that problems may have to be considered after instead of before they arise.

#### *Institutional Interest in Genetic Engineering*

Each time a new advancement in genetics or cell biology seems to bring some type of genetic engineering closer to reality, there is a reaction from the public which appears almost to border on real fear. The possibilities inherent in genetic engineering have resulted in a concern that there will be abuse as has occurred in certain applications of nuclear energy. The response many times has been a cry for prohibition of research. As noted in the preceding paragraphs, discussions on the synthesis of life become highly philosophical, as well as emotional, and include reactions to the religious and moral implications of new advancements. These fears may have an origin, in part, from the history of the development of the ideas of eugenics. Legislation taking its objectives from eugenic principles has been passed to prohibit marriage of individuals with inheritable defects; these laws

were followed by sterilization laws in some States and in other countries. Racist overtones have been present in eugenic discussions which have been even extended to the passage of immigration laws. Many of these actions, including the genocidal atrocities committed within Nazi Germany in the name of the development of a "master race," had little or no foundation in scientific fact.

The history of eugenics seems to emphasize the dangers inherent in the uncontrolled or poorly understood application or deliberate perversion of genetic principles. However, there is no similar history at this time to provide an evaluation of other types of genetic engineering. As Rollin D. Hotchkiss has presented the problem:

By contrast, the new potential program "genetic engineering", which is raised by the exploits of molecular biology, is a genetic intervention that could be practiced in private and in secret on individual genes of individual persons. I prefer to call it intervention since it may never be really engineering. It will be much more difficult to regulate, and legislation against it will seem like the same invasion of personal rights that legislation for eugenics measures appears to be. We have always been soft-hearted about a man's right to make a fool of himself, as long as he does not become a malicious fool. Yet this kind of intervention has more than a little potential for altering the gene pool from which all future humans will draw their imprint.<sup>10</sup>

Kurt Hirshhorn summarized the problem as follows:

I believe that the only logical conclusion is that all maneuvers of genetic engineering must be judged for each individual and, in each case, must take primary consideration of the rights of the individual. This is impossible by definition in any attempt at positive eugenics. Negative eugenics in the form of intelligent genetic counseling is the answer for some. Our currently unreasonable attitude about practicing negative eugenics by means of intelligent selection for therapeutic abortion must be changed. Basic to such a change is a more accurate definition of a living human being. Such restricted uses of negative eugencies will prevent individual tragedies. Correction of unprevented genetic disease, or that due to new mutation, by introduction of new genetic material may be one answer for the future; but until such a new world becomes universally feasible, we must on the whole restrict ourselves to environmental manipulations from both the points of view of allowing affected individuals to live normally and permitting each individual to realize his full genetic potential. There is no question that genetic engineering will come about. But both the scientists directly involved and, perhaps more important, the political and social leaders of our civilization must exercise utmost caution in order to prevent genetic, evolutionary and social tragedies.<sup>11</sup>

<sup>10</sup> Rollin D. Hotchkiss, Portents For A Genetic Engineering. *Journal of Heredity*, vol. 56, May 1965, p. 197-202.

<sup>11</sup> Kurt Hirshhorn, *op. cit.*, p. 261.

In an editorial prepared for *Science*, Dr. Marshall W. Nirenberg said:

The point which deserves special emphasis is that man may be able to program his own cells with synthetic information long before he will be able to assess adequately the long-term consequences of such alterations, long before he will be able to formulate goals, and long before he can resolve the ethical and moral problems which will be raised.

When man becomes capable of instructing his own cells, he must refrain from doing so until he has sufficient wisdom to use this knowledge for the benefit of mankind. I state this problem well in advance of the need to resolve it, because decisions concerning the application of this knowledge must ultimately be made by society, and only an informed society can make such decisions wisely.<sup>12</sup>

According to the *Medical Tribune*:

Means of genetic manipulation now available to clinicians are already posing ethical, legal and social problems and the issue will become more complex in the future \* \* \*<sup>13</sup>

Questions have been raised as well in regard to the selection of recipients of organ transplants, the assignment of kidney machines, the advice offered to individuals carrying deleterious genes for known diseases, and restrictions on abortions.

While this report is not intended to serve as an analysis of the complex philosophic questions of biomedical ethics, or the legal and moral issues, it is worthwhile at this time to mention the increasing interest in these aspects of all biomedical developments being evidenced in nongovernmental as well as government sectors. Many professional groups are attempting to define and develop policy level discussions for the resolutions of these biomedical issues, including specific emphasis on aspects of interest in genetic engineering. Perhaps best known among the more formal organizations are: the Institute of Society, Ethics, and the Life Sciences; the National Academy of Sciences Committee on the Life Sciences and Social Policy; the John E. Fogarty International Center for Advanced Studies in Health Sciences; the Joseph and Rose Kennedy Institute of Bioethics; the Council for Biology in Human Affairs of the Salk Institute for Biological Studies; and the American Medical Association Judicial Council.

The Institute of Society, Ethics, and the Life Sciences, Hastings-on-Hudson, N.Y., is a private interdisciplinary institute established to examine, among many questions, a primary question as posed by the Director, Daniel Callahan:

What ought society as a whole, and the professions in particular, do in the face of these issues (organ transplantation, human experimentation, prolongation of life, genetic engineering, etc.) and the problems they raise.<sup>14</sup>

<sup>12</sup> Marshall W. Nirenberg, Will Society Be Prepared? *Science*, vol. 157, August 11, 1967, p. 633.

<sup>13</sup> Medical Advances Already Posing Many Problems. *Medical Tribune*, April 24, 1967, p. 1, 14, 15.

<sup>14</sup> Daniel Callahan. Profile: Institute of Society, Ethics and the Life Sciences. *Bioscience*, vol. 21, July 1, 1971. Pp. 735-736.

The members of the Institute selected four major areas as warranting primary consideration. These were: ethics and population limitations; death and dying; behavior control; and genetic counseling and genetic engineering. As an indication of the interest in this latter area, the Institute co-sponsored with the Fogarty International Center, an international conference on "Ethical Issues on Genetic Counseling and the Use of Genetic Knowledge." The papers presented at this conference are being prepared in a special conference report and should be available by the fall of 1972. The genetic counseling and the genetic engineering groups of the Institute of Society, Ethics, and Life Sciences are under the direction of Co-chairmen Dr. James M. Gustafson, university professor of theological ethics, University of Chicago and Dr. Richard Roblin, Infectious Disease Unit, Massachusetts General Hospital. Dr. Marc Lappé, an associate for Biological Sciences at the Institute, is the program director. The Institute sponsors lectures and seminars on medical ethics, publishes reports on a regular basis, prepares research monographs, and offers a teaching program in medical ethics.

At the National Academy of Sciences, Dr. Milton Katz, Harvard Law School, is the chairman of the Committee on the Life Sciences and Social Policy. The committee has been engaged in a study of the assessment of biomedical technologies affecting such fields of research as in-vitro fertilization, determination of the sex of children, retardation of aging, and the modification of human behavior. According to Dr. Leon R. Kass, the executive secretary of the committee, the study is almost completed and after review will probably be available sometime early in 1973.

The Salk Institute, located at La Jolla, Calif., is well known for a number of advances in the field of molecular biology. Less well known is the fact that Dr. Jonas Salk has as one of his major objectives the establishment of the Institute as a National Center for the study of the impact of science on human affairs. Dr. Salk has been concerned for some time with the effect on society of the new developments in biology. To this end, the Institute has established a council for biology in human affairs which addresses such topics as the impact of new developments in genetic engineering.

The John E. Fogarty International Center for Advance Study in the Health Sciences, National Institutes of Health, Bethesda, Md., has as a major mission the coordination of discussion and conferences in biomedical, behavioral, and related fields in the life sciences. In performing this function, the center has been involved in the organization of conferences which have addressed problems in biomedical ethics and, as mentioned previously, recently sponsored a conference with the Institute of Society, Ethics, and the Life Sciences on problems in genetics.

The Joseph and Rose Kennedy Institute for the Study of Human Reproduction, and Bioethics, Georgetown University, was established in 1971. Dr. Andre E. Hellegers, the current head of the institute, envisions a permanent staff of professionals trained in the disciplines of human reproduction, social science and ethics. One of the first actions of the Kennedy Institute was to sponsor an "International Symposium on Human Rights, Retardation, and Research," held in Washington,

D.C., in October 1971. In addition to studies of bioethics by staff members, the Institute expects to continue to foster the exchange of information through similar symposia in the future. Dr. Leroy Walters is the director of the Kennedy Center for Bioethics at Georgetown.

The American Medical Association has provided for an exchange of views and the determination of policies in medical ethics through the actions of its Judicial Council. In addition, most hospitals provide biomedical ethics panels for the review and establishment of policies within the purview of immediate actions of the hospital. The major universities as well as an increasing number of law schools are providing for the exchange of ideas and evaluation of problems in the life sciences in such forums as the Institute For the Study of Science In Human Affairs, Columbia University; Institute For the Study of Health and Society, Washington, D.C.; Institute of Religion, Texas Medical Center; Interfaculty Program in Medical Ethics, Harvard University; and the Center for Law and Health Sciences at Boston University. As recently as May 1972, a symposium on genetic engineering was held by the biology department at the California Institute of Technology and a genetic engineering panel was convened at Worcester Polytechnic Institute. Particular attention has been addressed at these various meetings to such aspects as artificial insemination, abortion, the legal determination of death, transplantation of organs, the prolongation of life, and a consideration of the various implications of developments associated with genetic engineering.

A number of other organizations also are devoting more time to an open discussion for developing problems in the life sciences. The American Association for the Advancement of Science includes sessions which deal with ethical problems, schools of medicine are beginning to increase the scope of courses in the ethics of medicine and biology, departments of philosophy in the various colleges and universities are expanding their curricula of ethics courses to include new issues, and professional journals are devoting more publication space to articles which discuss all aspects of biomedical ethics. Commercial firms are becoming more involved as evidenced by a recent (1971) symposium on the challenge of life sponsored in Switzerland by the pharmaceutical firm of Hoffman-LaRoche. All of these activities indicate a rising trend of concern which will continue and increase in scope.

### *Legislative Concern*

The predictors of technological crises are beginning to cite developments in genetic engineering as having a special significance. As in other fields of science, some developments in genetic engineering have been more rapid than predicted, but also as in other areas of science some exaggeration of the rate of progress has occurred. The fact that genetic engineering seem to be approaching immediate application is adding to the depth of concern that legislative attention to the legal, ethical, and social implications of these developments is necessary. This concern has not gone unnoticed by the Congress.

In one of the more comprehensive discussions of the political problems of health sciences research, the U.S. Senate Committee on Government Operations held hearings in 1968 on a proposed National

Commission on Health Science and Society. The Commission was proposed as a forum for the investigation and study of the legal, social, and ethical implications of medical research. Although the primary emphasis of the hearings was on the problem of organ transplants, social and legal considerations of genetic engineering were discussed. Questions raised by Senator Ribicoff during the course of the hearings in regard to genetic engineering summarized many of the fears with regard to genetic engineering. He said:

Does science concern itself with the ethical, social and human consequences of its acts and achievements? How do we involve society and how do we involve the scientist in humane objectives in which people can live a decent, well-rounded life? Who makes the decisions? With genetic engineering, who are the beneficiaries, who makes the decisions as to who participates in genetic engineering? Is it widespread? Is it to everyone? Do we use it just to breed a master race?<sup>15</sup>

Statements made by other participants at these same hearings reflect the concern of scientists in various aspects of genetic engineering research. Dr. Lederberg, for example, said:

Many forms of compulsion are available to the state in its dealings with individuals. The perfection of biological engineering will add only a few minor subtleties to the existing repertoire of a totalitarian government. The only assurance we have for the preservation of individual dignity comes from a political system that minimizes the role of the state in private life. Indeed, the very guise of "protecting" individuals from the impact of new technology may cloak the most pernicious intrusions of the state into individual freedom. The state clearly has a role in insuring the liberty of individual decision and action in private matters to prevent and punish duress and deception, and to set the least intrusive limits demanded by social order.<sup>16</sup>

The problem of initiating legislation as new developments occur is not simple. As pointed out by Dr. John A. Anderson:

I am fearful that the problem of writing laws applicable to the hundreds of variable situations would be a formidable if not impossible task. Perhaps the following most recent experience concerning the establishment of a law which required the testing of the urine for identification of phenylketonuric patients, a form of mental retardation, may serve as an example of premature legislation. These laws now appear to be of doubtful value.<sup>17</sup>

And yet, at the time, the laws referred to by Dr. Anderson were considered to be well conceived and prompt in terms of insuring compliance with a new development in genetics of significance to the general welfare.

<sup>15</sup> U.S. Congress. Senate. Committee on Government Operations. Subcommittee on Government Research. Hearings on the National Commission on D.C. U.S. Govt. Print. Off., March 7, 8, 21, 22, 27, and 28; Apr. 2, 1968, p. 47.

<sup>16</sup> *Ibid.*, p. 61.

<sup>17</sup> *Ibid.*, p. 167.

More recently, the U.S. Senate, 92d Congress, first session, unanimously approved a resolution to establish a "National Advisory Commission On Health Science and Society." In commenting on this proposed legislation, Senator Walter F. Mondale said:

First, there is a growing awareness and concern throughout the country about the implications of biomedical advances. Second, significant breakthroughs may be very imminent. Science is not waiting for us, so we must move now if these issues are to receive the thorough examination they require.<sup>18</sup>

A companion bill in the House, H.R. 8279, was not considered. As already noted, the issue of genetic engineering received additional attention at the national level, when Dr. James Watson, Nobel laureate and one of the major speakers at the Panel of Science and Technology of the House of Representatives, selected this issue for the topic of his statement.<sup>19</sup>

Never before have the issues of abortion, euthanasia, organ transplantation, mental retardation, "heroic" medical measures such as the use of heart, lung, and kidney machines and similar topics been given such widespread publicity or discussed as frankly as has been the case in recent months. As a more specific example, the availability of mass screening techniques for the detection of certain inherited defects and the capability to determine the presence of genetic defects before birth have resulted in a pressing need to reevaluate many aspects of public health policy.

Attention to these biomedical issues also is being focused in a more direct fashion. For example, during the Senate HEW Appropriations Subcommittee hearings in May 1972 (for the fiscal 1973 budget) the Director of the National Institute of General Medical Sciences indicated that the institute was prepared to support grants dealing with ethics research, particularly genetic research. Biomedical ethics also have been highlighted in other appropriations hearings and have been the direct subject of attention during hearings held by both Senate and House Appropriations Committees on the general subject of public health.

The increasing awareness on the part of individual Members with regard to the overall problem of biomedical ethics is evidenced by membership on panels of institutions attempting to cope with these issues as well as by a willingness to write and speak on this problem. Most recently, for example, Senator John V. Tunney participated in a conference on genetic engineering at the California Institute of Technology and presented a paper entitled "The Impact of Genetic Engineering on Society."<sup>20</sup> He also introduced S. 3894, a bill calling for investigation into the social consequences of biomedical technologies. As indicated previously, the Senate passed unanimously its resolution to establish an advisory commission. The House did not consider H.R. 8279 on this same subject during the 92d Congress.

<sup>18</sup> U.S. Congress. Congressional Record. Senate. Apr. 29, 1971. P. S5912. (See also: Senate Report 92-517, 92d Cong., first sess. Report of the Committee on Labor and Public Welfare "National Advisory Commission on Health Science and Society." November 9, 1971).

<sup>19</sup> Panel on Science and Technology. Op. cit.

<sup>20</sup> U.S. Congress. Senate. Congressional Record. Health Science and Society. May 23, 1972. pp. S8230-S8233. (See also: John V. Tunney and Meldon E. Levine. Genetic Engineering. Saturday Review, Aug. 5, 1972, pp. 23-29).

## V. CONCLUSIONS

The science of genetics is rapidly moving out of the realm of theoretical research and into the more politically sensitive region of applied science. The technological capability to alter the course of human evolution is relatively close at hand. A need for assessment of this progress has already been identified and concern has been expressed that the point for making objective decisions may already have been passed for some of the issues.

An evaluation of the rate of progress in biomedical research is, at its best, a very speculative venture. Each step requires a foundation of knowledge that cannot be predicted as to a rate of accumulation. Each of a series of experiments unfolds new areas for investigation. The need for a high degree of certainty in any research on human beings generally tends to produce additional conservatism in approaches. However, it does appear that the rate of progress in genetic engineering is picking up and that several significant achievements may be expected within the next 8 to 10 years.

The possibility is very near that an externally fertilized human egg will be implanted surgically in a human uterus. The technique has been performed successfully in a limited number of specimens of a nonhuman primate. Concern is so great that this procedure will be performed on a human being that in-vitro fertilization has been a primary topic of debate in genetic engineering discussions. In April 1972, the American Medical Association announced that its Judicial Council would meet with a number of experts to discuss the ethical issues in medicine including genetic engineering problems.<sup>1</sup> In May, in an editorial, a plea was put forth to "declare a moratorium on experiments that would attempt to implant an in-vitro conceptus into a woman's womb."<sup>2</sup> As the most advanced research on this subject is proceeding in Cambridge, England, no legislative action in this country would legally influence the international work. The ethical concern being expressed by peer groups of scientists may have some influence on the rate of progress.

With regard to "gene therapy," the prospects look more speculative. S. E. Luria suggested some time ago that:

In medicine, we may envisage replacing the present treatment of genetic defects—for example, insufficient production of a hormone such as insulin—by supplying the proper gene to certain cells from the outside, or by implanting functional cells, or by causing the corresponding gene to become activated in other cells of the body which normally do not produce the hormone because of regulatory repressors.

<sup>1</sup> *Bioscience-Bioethics*. Journal of the American Medical Association, vol. 220, Apr. 10, 1972, pp. 272-273.

<sup>2</sup> *Genetic Engineering in Man: Ethical Considerations*. Journal of the American Medical Association, vol. 220, May 1, 1972, p. 721.

Manipulations of this kind could also, for example, alter the immunological reactions that cause the body to reject foreign tissues, an achievement that would make organ transplantation more successful.<sup>3</sup>

Other formal estimates indicate that it may be possible to achieve correction of a single gene defect within 5 to 10 years. Modification of multiple gene factors, such as intelligence or behavior, is still a speculation for the next several decades. The medical geneticist will use all of the available tools to combat and correct genetic deficiencies and possibly to prevent such deficiencies from occurring. As noted previously, an attempt is being made to correct a gene defect in human beings via a virus transfer technique.

The two prospects which have produced the most excitement, total cloning of man or total synthesis of man, are the least likely to occur in the near future. It is possible, according to some informal estimates, that cloning of mammalian cells following nuclear transplantation, as has been done with amphibians, may be achieved through some unexpected breakthrough. Total development with an artificial placenta and uterus is dependent upon a host of new technological developments.

The Office of Health Economics, London, has prepared a technological forecast which provides some information of the pace of events to be expected:

The greatest progress toward control of congenital abnormalities will come from a better understanding of their causes, and hence a greater ability to give "genetic counseling" to prospective parents. Over the next 20 years epidemiological studies will identify many new causative factors, the majority of them environmental. In addition, studies over several generations are likely to throw light on inbred genetic factors, such as those which cause porphyria. More accurate diagnoses of virus infections (such as rubella) during pregnancy should also increase the predictability of abnormalities. By 1980 we should see significant reductions in abnormalities due to a better understanding and easier identification of their causes. This may be supplemented by specific tests applied during pregnancy to determine whether the embryo at risk has been affected or not. This, however, presents very difficult problems.

For the abnormalities which still occur, better surgical treatment will be available for physically abnormal children, and replacement chemotherapy should be available to correct some inborn disorders of metabolism affecting brain function. It is not envisaged that any "molecular engineering" will be feasible on a routine basis by 1990, either to correct genetic abnormalities or to produce specific characteristics in the offspring. However, by then it should be possible to determine (and hence select) the sex of offspring during pregnancy. This could be particularly valuable in veterinary medicine.

On the negative side, vigilance will be needed to avoid accidental, harmful "molecular engineering" through the use of medicines or, for example, chemical additives to food.<sup>4</sup>

<sup>3</sup> S. E. Luria. *Modern Biology: A Terrifying Power*. The Nation, Oct. 20, 1969. P. 408.

<sup>4</sup> *Medicines in the 1990's, A Technological Forecast*. (Office of Health Economics, London, Alfred H. Cooper & Sons, Ltd., 1968), p. 10.

Any assessment of developments in genetic engineering will require an examination of more than just the extent and nature of research. Ethical, legal, economic, and political aspects require consideration as well as the biological problems. A separate evaluation may be required for those problems which may have an impact upon all society as compared with the events which are essentially personal or individual decisions (for example, a personal decision to utilize artificial insemination to alleviate infertility as compared with the capability to clone a human being).

The number of individuals and organizations concerned with genetic engineering is increasing and statements have been made already within the public forum calling for congressional attention to these problems. In today's climate of ecological concern with both the quality and quantity of life, developments in genetic engineering require careful study to arrive at socially acceptable policies.

The public demand for providing basic medical care to all will require additional and massive effort in medical genetics; the failure to provide such assistance is the source of resentment. The availability of new techniques in genetic engineering, with adequate consideration of all of the social and other implications, may add to this resentment rather than providing a panacea for genetic disease. One of the difficulties is that the intelligent use of many known genetic principles could undoubtedly relieve some of the pressing problems in long-term patient care by reducing the incidence of such patients. A major concern among some geneticists is that the failure to consider fully the available knowledge, and to apply this knowledge, is adding to the pool of undesirable genes and possibly accentuating medical problems for the care of individuals with various types of serious inherited defects.

Expansion of genetic counseling assistance seems to offer an immediate advantage in health care. Genetic counseling units have already been expanded from about 10-12 in the 1950's to more than 200 today. But at what point should the acceptance and application of such counseling be mandatory versus voluntary? Where these services have previously been limited to middle and upper class socioeconomic groups, the services will no doubt be further extended to include all who can profit from the service. The recent Federal support of genetic screening to detect the incidence of certain genetic disease (sickle cell anemia, for example) is evidence of this trend toward a growth in the number of genetic counseling centers. In view of the potential impact on society of national programs in genetic screening and counseling, this area in particular seems to warrant immediate review and evaluation.

The current concern with the population explosion and the evolution of such concepts as zero population growth is certain to produce pressures for evaluation of developments such as in-vitro fertilization. For example, what is the priority of research to provide for the correction of fertility problems in the face of pressure to reduce populations?

Any total assessment of the impact of developments in genetic engineering is going to require international participation eventually. A program related to this issue has already been recommended by a United Nations Group.<sup>5</sup> Research on these subjects is not limited to national borders; the exchange of information is improving as well as the capability for various nations to complete the required research. In fact, progress in certain areas of genetic engineering has been more rapid and uncontrolled in other countries.

In order to evaluate the impact of developments in genetic engineering, detailed information is needed as to at least: (1) The true extent of genetic disease; (2) the costs to society of caring for and maintaining genetically defective children (a determination of these costs will not be simple. It is very difficult to ascertain all of the factors which contribute to social costs as well as the effect of alternatives); (3) costs of treatment of diseases which are inherited; (4) the effect on public health policies of various options (counseling to prevent conception versus abortion of defective fetuses, for example); (5) legal considerations in human experimentation, abortion and artificial insemination; and (6) the ethical and psychological impact of these problems.

Agreement as to priorities for confronting these issues will require a more thorough and thoughtful appraisal of the estimates of the pace of developments in genetic engineering. Such an overall evaluation of genetic engineering will probably be one of the most complex and frustrating tasks ever attempted within the history of man. The alternatives would include an acceptance of the haphazard evolution of the techniques of genetic engineering, to hope that the issues will resolve themselves, or to continue to face such issues under pressure without the detailed knowledge that forethought and evaluation could provide.

In any event, as Donald Huisingh has pointed out:

The time ahead is uncharted. No one has been there, so there are no experts. Each of us whose body and brain may be modified or whose descendant's characteristics may be predetermined has a vast personal stake in the outcome. We can help to insure that good will be done only by looking to it ourselves. We must be careful to retain the individuality of the individual and the personality of the person, or else the humanity of the human may be lost.<sup>6</sup>

<sup>5</sup> Constance Holden. World Ethics Body Proposed. *Science*, vol. 177. Sept. 29, 1972. P. 1174.

<sup>6</sup> Donald Huisingh, *op. cit.* p. 198.

## APPENDIX 1

A very brief summary of the scientific progress leading toward the availability of genetic engineering techniques is provided in the following table. This table is not intended to be a comprehensive index of developments. The topics have been selected to illustrate progress and are not a list of the most important research experiments; many unlisted events in fundamental molecular biology have provided the foundation on which most of the selected topics are based.

TABLE 1.—A Chronological History of Events Selected to Illustrate Progress in Genetics Engineering<sup>1</sup>

Date	Event
1651	Concept that all living organisms originate from eggs.
1677	Sperm of man and other mammals observed.
1838	Cell theory developed.
1866	Publication of Mendel's "Experiments in Plant-Hybridization."
1869	Discovery of nucleic acids (Miescher).
1900	Mendel's research rediscovered.
1902	Chromosome theory of heredity presented.
1909	Earliest study of biochemical genetics.
1927	Induction of mutations with X-rays.
1933	Theory of gene.
1941	Classical study on biochemical genetics of <i>Neurospora</i> .
1950	Foundation work for nucleic acid studies.
1952	Transplantation of nuclei into enucleated frog's eggs.
1953	Model for DNA proposed.
1956	In vitro synthesis of ribonucleotides and deoxyribonucleotides. In vitro cloning of human cells.
1959	Chromosome relationships to diseases: Turner's Klinefelter's, and Down's syndromes.
1961	Clawed toad cloning. Messenger RNA code solved, genetic language explained.
1962	Specific genetic message isolated.
1963	In vitro fertilization of hamster egg. In vitro culture of human cells in solution.
1968	In vitro fertilization of mouse eggs, transplantation in utero, 17-day-old fetuses obtained.
1969	Experimental parthenogenesis in the mouse, development to parthenogenetic mouse blastocysts. Human eggs matured in vitro, fertilized in vitro, development studies.

See footnote at end of table, p. 46.

TABLE 1.—A Chronological History of Events Selected to Illustrate Progress in Genetics Engineering<sup>1</sup>—Continued

Date	Event
1970	<p>In vitro fertilization and cleavage of human oocytes. First complete synthesis of a gene (bacterial). Insertion of chick genetic material into mouse nucleus.</p> <p>Improvement in techniques for extracting and inserting chromosomes into human cells. Bacteriophage transduction in human cells. In vitro fertilization of mouse eggs, culture to blastocyst stage, implantation, development to normal offspring. Female offspring derived from in vitro fertilization mated and developed of normal progeny.</p>
1971	<p>Experimental freezing of fertilized mouse ova. In vitro fertilization of mouse eggs, in vitro implantation of 3-day-old embryos on rat-tail collagen with survival up to 14 days. Partial development of opossum fetuses grown in culture.</p>

<sup>1</sup> Adapted in part from Robert C. King. Dictionary of Genetics. (New York, Oxford University Press, 1968) and many other reports of research in the literature.

## APPENDIX 2

### SELECTED BIOGRAPHIES OF INDIVIDUALS INVOLVED IN VARIOUS ASPECTS OF GENETIC ENGINEERING<sup>1</sup>

- Aposhian, H. Vasken. B.S., Brown, 48; fellow, Rochester, 49-54, M.S., 51, Ph. D. (physiology), 54. Assistant, Rochester, 48-49; instructor pharmacology, School of Medicine, Vanderbilt, 54-56, Assistant Professor, 56-59; U.S. Public Health Service fellow, Biochemistry, Stanford, 59-62; associate professor of microbiology, School of Medicine, Tufts University, 62-; School of Medicine, University of Maryland. Enzymology of deoxyribonucleic acid and its precursors; biochemistry of bacterial and animal virus infection. Address: School of Medicine; University of Maryland, Baltimore, Md.
- Axelrod, David Robert. University of Connecticut, 41-43; University of New Hampshire, 43-44; M.D., New York University, 48. Research fellow, physiology, Medical College, Syracuse, 49-50; research associate, physiology, Medical College, Cornell University, 50-52, assistant professor, 55-66; Clinical Associate Professor of Medicine, State University of New York, Downstate Medical Center, 70-. Electrolyte metabolism. Address: VA hospital, 800 Poly Place, Brooklyn, N.Y. 11209.
- Callahan, Daniel. B.A., Yale, 52; M.A., Georgetown, 57; Ph. D., Harvard, (philosophy), 65. Teaching fellow, General Education, Harvard, 57-61; teaching fellow, Roman Catholic Studies, Harvard Divinity School, 59-61; visiting professor of religion, Temple, 61; visiting professor of religious studies, Brown, 65; visiting professor of theology, Marymount, 67; professor in summer session, Graduate Theological Union, Berkeley, 68; visiting professor in ethics, University of Pennsylvania, 70; executive editor, Commonweal, 61-68; staff associate, Population Council, 69-70; director, Institute of Society, Ethics and the Life Sciences, 69-. Ethical issues in genetic counseling and the use of genetic knowledge; theology; ethics and population; ethics, law and public morality; meaning of genetic disease. Address: Director, Institute of Society, Ethics and the Life Sciences, 623 Warburton Avenue, Hastings-on-Hudson, N.Y.
- Crow, James Franklin. A.B., Friends, 37; Ph. D. (genetics), Texas, 41. Tutor zoology, Texas, 37-40; instructor, Dartmouth College, 41-44; assistant professor of zoology and preventive medicine, Medical School, 44-48; Zoology and Genetics, University of Wisconsin, 48-50; associate professor, 50-54; professor 54-58, medical genetics, 58-; acting dean of medical school, 63-65; chairman of Department of Genetics and Medical Genetics, 65-70. Genetics of *Drosophila*; population genetics. Address: Department of Genetics, University of Wisconsin, Madison, Wis. 53706.
- Danielli, James F. B. Sc., University College, London, 31, Ph. D. (chemistry), 33, D. Sc. (physiology), 38; Princeton, 33-35; Ph. D. (biochemistry), Cambridge, 42; hon. Sc. D., Ghent, 56. Physiologist, Marine Biology Association, 45-46; Reader Cell Biology, Royal Cancer Hospital, University of London, 46-49, professor and chairman of Department of Zoology, Kings College, 49-62; Biochemistry-Pharmacology, State University of New York at Buffalo, 62-. Cell Biology, surface science; theoretical biology, physiology; chemotherapy. Address: Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, N.Y.

<sup>1</sup>The biographies are intended to provide only a representative list of individuals in the United States with a history of research or other involvement in genetic engineering and related fields as well as having expressed their "thoughts" concerning the political, social, ethical, and economic issues associated with genetic engineering. The list is by no means to be considered complete or comprehensive. An examination of footnote references in the text and authors in the bibliography will identify other individuals. Sources of biographical data include American Men and Women of Science (Jaques Cattell Press, New York, 1971) as well as personal communications. Addresses are based upon the most recent available information.

- Davis, Bernard D. A.B., Harvard University, 36, M.D., 40. Research fellow and intern, Johns Hopkins, 40-41; commissioned officer, U.S. Public Health Service, 42-54; professor of pharmacology, College of Medicine, New York University, 54-57; bacteriology and immunology, Harvard Medical School, 57-68; Adele Lehman, professor of bacteriology-physiology and director of unit, 68-. Microbial metabolism and genetics; chemotherapy. Address: Bacterial Physiology Unit, Harvard Medical School, Boston, Mass. 02114.
- Dyck, Arthur J. B.A. (sociology), Tabor College, 53; M.A. (psychology), Kansas, 58, M.A. (philosophy) Kansas, 59; Ph. D., (religious ethics) Harvard, 66. Research assistant in psychology at the University of Kansas, 57-60; special lecturer in philosophy at the University of Saskatchewan, 64-65; assistant professor of social ethics at the Harvard Divinity School and a member of the Harvard Center for Population Studies, 65-69; Mary B. Saltonstall professor of population ethics, Harvard School of Public Health, 69-. Address: Department of Population Sciences, Harvard School of Public Health, 665 Huntington Avenue, Boston, Mass. 02115.
- Erbe, Richard, B.S., University of Michigan, 60; M.D., Michigan, 64. Intern, Peter Bent Brigham, Boston, 64-65; assistant research in medicine, 65-66; Research associate, Laboratory of Biochemistry, National Cancer Institute, NIH, 66-68; research fellow in Biological Chemistry, Harvard Medical School, and assistant in medicine, Peter Bent Brigham Hospital, Boston, 68-70; Instructor in Pediatrics, Harvard, 70-72; Assistant in pediatrics and medicine, Massachusetts General Hospital, 70-; Attending in medicine (genetics), VA hospital, West Roxbury, 70-; assistant professor of pediatrics, Harvard, 72-. Genetic engineering; molecular biology, protein and enzyme chemistry, biochemical genetics; normal and abnormal regulation of metabolic enzymes in humans; genetic counseling. Address: Harvard Medical School, Massachusetts General Hospital, Genetics Unit, Boston, Mass. 02114.
- Ehrman, Lee. B.S., Queens College (N.Y.), 56; M.A., Columbia, 57; Ph. D. (genetics), 59. Lecturer of zoology, Barnard College, 56-58; U.S. Public Health Service fels. genetics, Columbia, 59-62; research associate, population genetics, Rockefeller University, 62-64, Assistant Professor, 64-; associate professor of natural science, State University of New York at Purchase, 71-. Natural reproductive isolating mechanisms, especially hybrid sterility and sexual behavior isolation; cytoplasmic inheritance. Address: Division of Natural Sciences, State University of New York at Purchase, Purchase, N.Y. 10577.
- Fletcher, Joseph. A.B., West Virginia University, 25; B.D., Berkeley Divinity School, 29; S.T.D., University of London, 32, 39; hon. Litt. D., Ohio Wesleyan; hon. D.D., Berkeley Divinity School. Social research director, Episcopal Church National Council, 27-29; lecturer, Charles Kingsley Labor College (London), 29-31; instructor and chaplain, St. Mary's Junior College, 32-35; Dean, St. Paul's Cathedral, Cincinnati, 36-41; dean, Graduate School of Applied Religion, Cincinnati, 36-44; lecturer, University of Cincinnati, 38-42; Professor, Episcopal Theological School, Cambridge, Mass., 44-70; Director, Musser Seminar, Harvard Business School, 62-67; visiting professor, medical ethics, University of Virginia, 70-Address; School of Medicine, Box 358, University of Virginia, Charlottesville, Va. 22901.
- Fox, Allen S. B.S., Chicago, 41, Ph. D. (zoology), 48. Assistant professor of zoology, Ohio State University, 48-52; Fulbright professor, Pavia, Italy, 53-54; associate professor of zoology, Michigan State University, 54-59; from associate professor of agricultural chemistry to professor of biochemistry, 59-63; Genetics, University of Wisconsin, 63-. Biochemical and developmental genetics; immunogenetics; protein synthesis, tissue culture; differentiation; transformation *Drosophila*, *Neurospora*. Address: Laboratory of Genetics, University of Wisconsin, Madison, Wis. 53706.
- Friedmann, Theodore. A.B., University of Pennsylvania, 56 M.D., 60; University of Cambridge, 63-64. Intern (pediatrics) Children's Hospital (Boston), 60-61, resident, 61-62; University of Cambridge research fellow, 63-64; senior resident, Children's Hospital (Boston) 64-65, fellow in pediatrics, 65; fellow in Laboratory of chemical biology, NIAMD, 65-67, medical officer, Laboratory of Human Genetics, NIAMD, 67-68; Medical Officer Laboratory of Clinical Biochemistry, NHI, NIH, and the Salk Institute for Biological Studies, post-doctoral fellow. 68-69; University of California assistant professor of pediatrics, 69-. Human genetics and tumor virology. Address: Department of Pediatrics, School of Medicine, University of California, San Diego, P.O. Box 109, LaJolla, Calif. 92037.

- Green, Harold P. A.B., Chicago, 42, J.D., Chicago, 48. Practiced law in Chicago, 48-50; Office of the General Counsel of the U.S. Atomic Energy Commission (D.C.), 50-54; acting counsel to the Subcommittee on Reorganization, Senate Committee on Government Operations, 55; professor of law and director of the law, science and technology program, George Washington University, 64-. Address: National Law Center, The George Washington University, Washington, D.C. 20006.
- Hafez, Saad Elsayed. B. Sc., Cairo, 42; Ph. D. (physiology of reproduction), Cambridge, 51. Instructor, Cairo, 42-47, senior lecturer, 52-55; research investor, Cambridge, 47-52; research fellow, physiology of reproduction, Worcester Foundation Experimental Biology, 55-56; visiting research fellow-Institute of Experimental Spermatology, Italy, 57; visiting professor, Washington State, 57-58; associate professor of animal science, 58-65; professor of animal physiology. Reproduction and the physiology of farm animals; ova transplantation; animal behavior; cytogenetics; animal ecology. Address: Wayne State University, Detroit, Mich.
- Hellegers, Andre E. Stonyhurst College (England), 40-44; Edinburgh University Medical School, 44-51; L.R.C.P., L.R.F.P.S., 51; Belgian National Boards, Brussels, M.D., 52; Diploma of Aviation Medicine, Paris University, 52. Intern to associate professor, Johns Hopkins, 53-67; Josiah Macy research fellow in Physiology, Yale, 56-57; lecturer in population dynamics, Johns Hopkins, 66-; professor, Georgetown University, 67-; Director of Population Research and of Kennedy Institute, Georgetown University, 71-. Address; Kennedy Institute for Population Studies, Georgetown University, Washington, D.C.
- Hirschhorn, Kurt. M.D., N.Y. University, 54; M. Sc. in International Med., NYU, 58. U.S. Public Health Service Trainee (NYU), 56-57; advanced research fellow, 58-60; established investigator, 60-65; (AHA) assistant attendant 59-64; Associate attendant, 64-66 (U Hospital, NYC), Career Research Scientist (NYC Health Research Council) 66-, attendant pediatrics (Mount Sinai Hospital, 66-, assistant professor of Internal Medicine, 59-64; associate professor, 64-66 (NYU), professor of Pediatrics and Chief of Division of Medical Genetics, (Mount Sinai School of Medicine) 66-. Address; 100th Street and 5th Avenue, NYC.
- Kaback, Michael M. B.A., Haverford, 59; M.D., University of Pennsylvania, 63; intern, pediatrics, Johns Hopkins Hospital, 63-64; research associate, Laboratory of Molecular Biology, National Institute of Neurologic Diseases and Blindness, 64-66; assistant resident, pediatrics, Johns Hopkins Hospital, 66-67; senior assistant resident, pediatrics, Johns Hopkins Hospital, 67-68; research fellow, Department of Pediatrics, Johns Hopkins Hospital, 66 and 68; instructor, Department of Pediatrics, Johns Hopkins School of Medicine, 68-69; assistant professor and Pediatrician, Johns Hopkins Hospital, 69-72; member, active staff, John F. Kennedy Institute, 70-72; attending physician, Sinai Hospital, 70-72. In-vitro culture mammalian cells; mechanisms of genetic regulation and cellular differentiation; applications of molecular biochemical techniques to detection and study of human genetic-metabolic disorders; intrauterine diagnosis of severe human genetic disorders; community genetic education, screening, and counseling. Address: Associate Professor of Pediatrics (UCLA), Department of Pediatrics, Harbor General Hospital, 1000 West Carson Street, Torrance, Calif. 90509.
- Kass, Leon Richard. B.S. Chicago, 58; M.D., 62; NIH fellow, Harvard, 63-67; Ph. D. (biochemistry, molecular biology), 67. Internal medicine, Beth Israel Hospital, 62-63; staff associate, molecular biology, NIAMD, 67-69; senior staff fellow, 69-. Fatty acid biosynthesis in bacteria; deoxyribonucleic acid replication and segregation of episomes, plasmids and temperate bacteriophage; ethical problems in medicine and biology. Address: executive secretary, Committee on Life Sciences and Social Policy, National Academy of Sciences, Washington, D.C.
- Khorana, Har Gobind. B. Sc. Punjab, India, 43, M. Sc., 45, Ph. D., Liverpool, 48. Government of India fellow with Prof. V Prelog Swiss Federal Institute of Technology, 48-49, Nuffield fellow, with Professor Sir Alexander Todd. Cambridge, 50-52; head organic chemistry group, British Columbia Res. Couns. and resident professor, faculty graduate studies, British Columbia, 52-59; professor and group leader, Institute of Enzyme Research, Wisconsin, 60-, Conrad A. Elvepheim, professor of life sciences, 64-, Nobel Prize in Medicine, 68. Address: Institute of Enzyme Research, University of Wisconsin, Madison, Wis. 53706.

- Lappé Marc. B.A., Wesleyan, 64; Ph. D., University of Pennsylvania (experimental pathology); Post-doctoral work at University of California at Berkeley, pre-graduate experience in research at Jackson Laboratory and Rockefeller Institute, student at Weizman Institute, 62-63; acting assistant professor in zoology, Berkeley, 70-71; Institute of Society, Ethics and Life Sciences (associate for the biological sciences), 71-. Genetic engineering, mass genetic screening. Address: Institute of Society, Ethics, and the Life Sciences, 623 Warburton Avenue, Hastings-on-Hudson, N.Y. 10706.
- Lederberg, Joshua. B.A., Columbia, 44; Ph. D. (microbiology), Yale, 47, Sc. D., 60. Assistant professor genetics, Wisconsin, 47-50, associate professor, 50-54, professor, 54-58, professor of medicine and genetics, 58-59, professor of genetics and biology and executive head of Department of Genetics, Nobel Prize in Medicine, 58, Medical School, Stanford, 59-, Director Kennedy Labs of Molecular Medicine 62-. Genetics and evolution. Address: Department of Genetics, Stanford University School of Medicine, Palo Alto, Calif. 94304.
- Mastroianni, Luigi, Jr. A.B. Yale, 46; M.D. Boston, 50. Resident fellow in infertility and endocrinology, Harvard Medical School, 54-55, instructor, obstetrics and gynecology, 55-56; assistant professor of school of medicine, Yale, 56-61; professor California, Los Angeles, 61-65; professor and chairman of department, Pennsylvania, 65-. Human infertility; reproductive physiology. Address: University of Pennsylvania Hospital, 3400 Spruce St., Philadelphia, Pa. 19104.
- Mayr, Ernst. Ph. D. (zoology), Berlin, 26; honorary D. Phil, Uppsala, 57; honorary D. Sc., Yale, 59; Melbourne, 59, Oxford 66. Assistant curator of zoological museum, Berlin, 26-32; Associate curator Whitney-Rothchild collection, American Museum Natural History, 32-44, curator, 44-53; Agassiz professor zoology, Harvard 53-; Director of Museum of Comparative Zoology, 61-. Ornithology, zoogeography; evolution. Address: Museum of Comparative Zoology, Harvard University, Cambridge, Mass. 02138.
- McKusick, Victor Almon. Tufts, 40-43; M.D., Johns Hopkins, 46. Intern Medicine, Hopkins Hospital, 46-47, assistant resident, 47-48; researcher, U.S. Public Health Service, 48-50; intern. medicine, Hopkins Hospital, 50-51, physician, 53-, chief of Division of Medical Genetics, 57-, professor of medicine, Medical School of Johns Hopkins, 60-, medical genetics; cardiology. Address: Division of Medical Genetics, Johns Hopkins Hospital, Baltimore, Md.
- Mellman, William J. M.D., Pennsylvania, 52. Intern, 52-63; staff pediatrician (Philadelphia General Hospital), resident pediatrician 55-58, staff pediatrician (Hospital of University of Pennsylvania), fellow endocrinology, 57-58, staff pediatrician (Children's Hospital) associate professor of pediatrics, University of Pennsylvania. Address: University of Pennsylvania Hospital, 3400 Spruce St., Philadelphia, Pa. 19104.
- Merril, Carl R. B.S., College of William and Mary, 58; M.D., Georgetown University, 62. Student fellowships in biochemistry and cardio-pulmonary physiology, Georgetown, 58-62; internship, U.S. Public Health Service Hospital in Boston; National Institutes of Mental Health (molecular biology); senior research Scientist in the Laboratory of General and Comparative Biochemistry at the National Institute of Mental Health intramural research program, molecular biology. Address: National Institute of Mental Health Intramural Research Program, Bethesda, Md. 20014.
- Mertz, Edwin T. A.B., Montana, 31; M.S., Illinois, 33, fellow, 34-35, Ph. D. (biochemistry), 35 Assistant chemist, Illinois, 31-34, Instructor biochemistry, 37-38; Research chemist, Armour & Co., 35-37; research associate pathology, Iowa, 38-40; Instructor of agricultural chemistry, Missouri, 40-43; research chemist, experimental station, Hercules Powder Co., Delaware 43-46; assistant professor of Agricultural Chemistry, Purdue, 46-50, associate professor of Biochemistry, 50-57, professor, 57-. Physiology and chemistry of hemostasis; amino acid requirements of humans and animals; isolation and purification of plant and animal proteins; biochemistry of mental retardation; opaque-2 and floury-2 (high lysine) maize. Address: Department of Biochemistry, Purdue University, West Lafayette, Ind. 47907.
- Mizell, Merle. B.S. Illinois, 50 M.S., 52, Ph. D. (zoology) 57. Instructor of zoology, Tulane, 57-60, assistant professor, 60-64, associate professor of biology 64-. Cellular and tumor differentiation vertebrate regeneration; viral theory of carcinogenesis; induction of mammalian limb regeneration. Address: Department of Biology, Tulane University, New Orleans, La. 70118.

- Motulsky, Arno G. M.D., Illinois, 47. Rot. intern 47-48; fellow Department of Hematology, 48-49; assistant and senior researcher, Department of Medicine, 49-51 (all at Michael Reese Hospital, Chicago), clinical investigator, Department of Hematology (Walter Reed Army Medical Center, Washington DC), 52-53; attending physician (Kings College Hospital) (University Hospital) (VA Hospital) (Children's Hospital, Seattle), 54-, Research Associate Department of Medicine (George Washington), 52-53, instructor Department of Medicine, 53-55, assistant professor, 55-58, associate professor, 58-61, professor, 61-. Address: Department of Medicine, University of Washington, Seattle, Wash.
- Murray, Robert F., Jr. M.D., University of Rochester School of Medicine, 58; fellow in medical genetics at the University of Washington School of Medicine, 65-7, M.Sc. (genetics), 65-67. Staff investigator at NIH in the biometry branch of the National Institute of Arthritis and Metabolic Disease; Assistant Professor of Pediatrics and Medicine at Howard University College of Medicine, 67, chief of the Medical Genetics Unit, 68; fellowship, Institute of Society, Ethics, and the Life Sciences; associate professor of pediatrics and medicine at Howard University College of Medicine, 70-.
- Nagle, James J. King's College, 58-59, B.S., Bloomsburg State College (Penn.), 62; M.S., North Carolina State, 65; Ph. D., 67. Teaching Assistant, North Carolina State, 65-66; instructor, 66-67; N.D.E.A. fellowship, 64-67; associate editor, bulletin of the New Jersey Academy of Sciences, 72-; associate professor of zoology and botany, Drew University, 67-. Population genetics and evolution with *Drosophila*; human genetics and its social implications. Address; Department of Zoology, Drew University, Madison, N.J. 07940.
- Nirenberg, Marshall W. B.S., Florida, 48, M.S., 52; Ph. D. (biochemistry), Michigan, 57, hon. D. Sc., 65; hon. D. Sc., Chicago, 65, Yale, 65. Assistant zoologist, Florida, 45-50; research associate, Nutrition Lab, 50-52; fellow, biochemistry, Michigan, 52-57; fellow, American Cancer Society, National Institute of Arthritis and Metabolic Diseases, 57-59; fellow, Public Health Service, sect. metabolic enzymes, 59-60; research biochemist, 60-62; head of section on chemical genetics, National Heart Institute, 62-66; research biochemist and chief biochemist of Genetics Lab, 66-. Nobel prize in medicine, 68. Address: Laboratory of Biochemical Genetics, National Heart Institute, Bethesda, Md. 20014.
- Ramsey, Paul. B.S., Millsaps, 35; B.D., Yale, 40; Ph. D., Yale, 43; hon. Sc. D., Worcester Polytechnics Institute, Worcester, Mass. Taught history, social science and philosophy at Millsaps, social philosophy at Yale, and Christian ethics at Northwestern (Garrett Seminary), assistant professor of religious thought, Princeton; associate professor, Princeton, 47, professor, 54, Harrington Spear Paine Chair in Religion, 57; senior fellow in the Council of Humanities, 58-59; president of American Society of Christian Ethics in the United States and Canada, 62-63; president of the American Theological Society, 64-65; Joseph P. Kennedy, Jr. Foundation, visiting professor of genetic ethics, 68-69; presently is Paine professor of religion at Princeton University. Address: Department of Religion, Princeton University, Princeton, N.J. 08540.
- Sinsheimer, Robert L. B.S., MIT, 41; M.S., 42; Ph. D. (Biophysics), 48. Staff member, Radiation Lab., MIT, 42-46; American Cancer Society fellow, MIT, 46-48; research associate, biology, MIT, 48-49; associate professor of biophysics, Iowa, 49-55; professor of biophysics, Iowa, 55-58; professor of biophysics, California Institute of Technology, 57-; chairman, Division of Biology, CIT, 68-. Physical and chemical properties of nucleic acids; replication of nucleic acid; bacterial viruses; biological effects of ultraviolet radiation; biological applications of ultraviolet and infrared spectroscopy. Address: Division of Biology, California Institute of Technology, Pasadena, Calif. 91109.
- Sorenson, James R. B.A., University of Washington, 65, M.A., 66; Ph. D., Cornell, 70; research fellow, Institute for Sociological Research (U. Wash), 66; research fellow, Social Psychology Lab., Cornell, 68-69; assistant professor of sociology, Princeton, 69-; principle investigator, research project on genetic counseling, Russell Sage Foundation, 70-72; principle investigator, genetic counselors: professionals in applied human genetics, 72-73. Address: Department of Sociology, 2-N-2 Green Hall, Princeton University, Princeton, N.J. 08540.

- Speigelman, Sol. B.S., City College, NY, 38; Columbia, 40-42; Ph. D., (biology), Washington (St. Louis), 44; hon. D.Sc., Northwestern, 66; Rensselaer Polytech., 66. Lecturer mathematics and mechanics, Washington (St. Louis), 42-44; general physiologist, 43-44; instructor medical bacteriology, medical school, 44-45; assistant professor, 45-48; U.S. Public Health Fellow, Medical School, Minnesota, 48-49; professor of microbiology, Illinois, 49-. Adaptive enzymes; genetics and biochemistry of microorganisms; mechanisms of gene action; embryology; cellular physiology; protein and nucleic acid synthesis. Address: Department of Microbiology, University of Illinois, Urbana, Ill. 61801.
- Watson, James Dewey. B.S., Chicago, 47; Ph. D., Indiana, 50; hon. D.Sc., Chicago, 61; Indiana, 63; LL.D., Notre Dame, 65. Natural resources council fellow, Copenhagen, 50-51; Cambridge, 51-52; National Foundation for Infantile Paralysis fellow, 52-53; senior research fellow in biology, California Institute of Technology, 53-55; assistant professor of biology, Harvard, 56-58; associate professor, 58-61; professor, 62-; co-recipient of Nobel Prize in medicine, 62. Bacteriophage reproduction; structure of the nucleic acids; protein synthesis. Address: Department of Biology, Harvard University, Cambridge, Mass. 02138.

## APPENDIX 3

### SELECTED READINGS IN GENETIC ENGINEERING

#### A. GENETIC ENGINEERING: THE MODIFICATION OF MAN\*

(By Robert L. Sinsheimer<sup>1</sup>)

The rapidly moving field of molecular biology will soon provide man with the capability of overruling the constraints of heredity and even of controlling human evolution. At first, this capability will be used to correct maladies of genetic origin in existing persons—diabetes, here discussed, may provide an early example.

But eventually we will be able to design human beings to plan, providing the unborn with a desired genetic makeup. This ability to make man over has enormous implications, good and bad, for the future of our species, Professor Sinsheimer, aware of both, argues strongly that we must take advantage of this promise of shattering the evolutionary limitations of the human race.

Today we can envisage the possibility of the deliberate and controlled modification of the genetic makeup of man—of “genetic engineering.” This possibility takes two forms: one is to make changes in the genetic makeup of cells in the bodies of already existing individuals. This mode of change, the somatic one, would have applications for the treatment of hereditary defects affecting an individual’s health and well-being. In this case, the changes made would not be transmittable to offspring.

The second is for the predesign of the genetic makeup of unborn children. This, the strictly genetic mode, could be used to modify hereditary human characteristics, to create humans matching some preconceived pattern or model; it has obvious applications for either good or bad, depending on who conceives the model or pattern. The characteristics “engineered” into the new individual would be transmittable to offspring according to the well-known laws of genetics.

Designed genetic change in the somatic mode has much greater near-term possibilities than that in the strictly genetic mode. Neither, however, is for the immediate future in the opinion of most molecular geneticists, who are aware that, rapidly as we have moved in this field, there are still a great many dark areas in the fabric of our knowledge which must be illuminated before we can actually undertake genetic manipulations on humans.

Yet, perhaps, one should hedge. The history of science and technology, particularly in the 20th century, has demonstrated that scientists have been consistently wrong—often far wrong, and generally on the conservative side—in predicting the pace at which the new

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<sup>1</sup> Molecular biologist Robert L. Sinsheimer is Chairman of the Division of Biology, California Institute of Technology, Pasadena, California 91109 (United States).

knowledge acquired by scientific research has been converted into practical applications. In predicting that "genetic engineering" is still some time away, my fellow molecular biologists and I may be repeating the same error of underestimation. Certainly, remarkable advances, exciting new discoveries, are being made in this vigorous and dynamic discipline every day, and indeed, this paper may well be obsolete in details by the time it reaches print.

A striking evidence of the rapidity with which molecular biology is evolving, and of the fundamental scientific importance of its discoveries, is the list of Nobel Prize winners in the category of physiology and medicine which has been dominated since the 1950s by researchers in this field.

However near the time may be at which we will start doing it, I think this possibility of making deliberate genetic changes in man is potentially one of the most important concepts to arise in the history of the race. I can think of none with greater long-range implications for the future of our species. Indeed, this concept marks a turning point in the whole evolution of life. Even in the ancient myths man was constrained by his essence. He could not rise above his nature to chart his destiny. This day we can envision that chance and choice.

In this article my technical emphasis will be on the possibilities of designed changes in the somatic mode, since this has much greater near-term possibilities. However, I will also deal with the promise, implications and problems of creating or modifying new human beings to a preconceived design, in the strictly genetic mode. Before proceeding to the heart of the discussion, I should like to review briefly the way the genetic mechanism functions at the molecular level.

#### HOW THE GENES EXPRESS THEMSELVES

Classical genetics postulated, from experimental observations, the existence of a basic unit of heredity, the gene. Large numbers of genes are linked together, like the beads on a necklace, to form the macro-unit of heredity, the chromosome. The chromosomes, large enough to be observed under the optical microscope, are carried in the nuclei of the cells of every plant or animal, the number of chromosomes differing for each species.

While classical genetics could postulate the existence of these basic hereditary units it had no means of explaining the mechanism by which the genes—probably millions of them in highly evolved animals and plants—control hereditary traits. This explanation was made possible by the evolution of molecular genetics in the past 30 years.

We now know that the genetic substance of the chromosome is composed of extremely long molecules of deoxyribonucleic acid (DNA) and that the genes represent tracts along such molecules.

Classical genetics had considerable difficulties in defining a gene precisely, since it was observed, experimentally, not only that one "gene" could be involved in determining several hereditary traits but also that several "genes" could be involved in defining a single hereditary trait.

Molecular biology now enables us to define the gene more incisively. We now say that a gene is the hereditary unit which specifies the structure of one of the vital biochemical components of the cell. These vital biochemical components often, but not always, are proteins. Such a protein may be an enzyme (a biochemical catalyst—a catalyst is a substance which causes a chemical reaction involved in either synthesis or decomposition to proceed) or a structural protein (one used in the framework or surface of the cell or body). An individual protein molecule is often composed of a single folded chain of small sub-units, called amino acids. Some 20 different amino acids are used in various proportions and sequences to make up the various proteins.

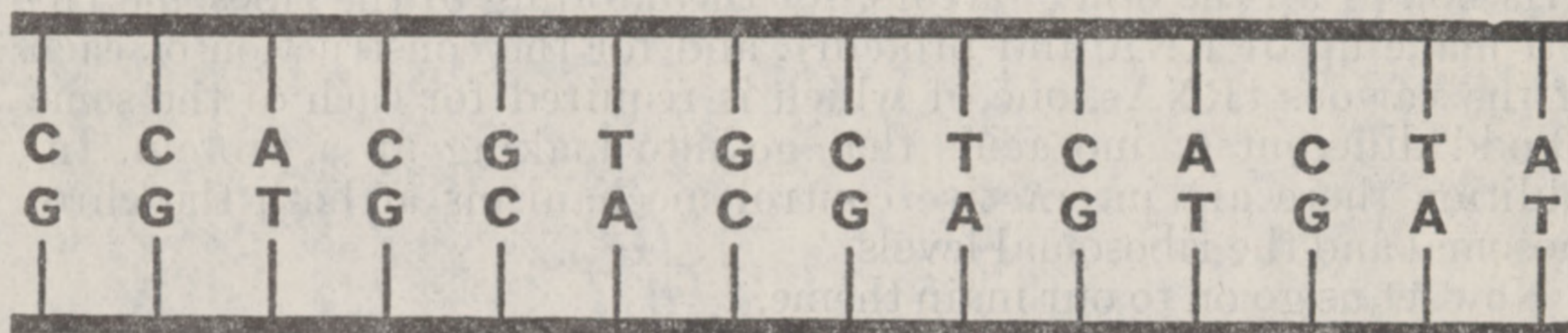


FIGURE 1.—A segment of DNA, when uncurled, has a ladder-like form. It is made up of two “spines,” with bases (A, G, C, T) attached along the length of each.

The work of James Watson and Sir Francis Crick, which won the Nobel Prize for 1962, revealed that DNA takes the form of the famous double helix. If we were to uncurl the double helix and stretch it out we could see that it has a ladder-like form (fig. 1). Looking at just one-half of the ladder, it can be seen that it consists of a long spine (the “side” of the ladder), to which are attached, at regular intervals, molecules of only four different chemical types, called bases (the “half-rungs”). A base, taken together with the segment of the “side” to which it is attached, is called a nucleotide. The four bases are adenine (A), thymine (T), guanine (G) and cytosine (C).

The other half-ladder is simply a complement of the first because each base on a half-ladder is always matched with a specific base on the other half-ladder: T only associates with A, and G only associates with C. Thus, knowing the structure of one half-ladder one immediately knows the structure of the other.

Structurally speaking, a gene can now be stated to be a segment of the much larger DNA molecule. A gene may contain anywhere from around 70 to several thousands of base pairs, and its beginning and end are clearly delimited by certain markers.

How does a gene express itself? First in the cell nucleus one of its two DNA strands acts as a template along which forms a complementary strand of another closely related nucleic acid, ribonucleic acid (RNA); this is complementary in just the same way as the other DNA strand of the double helix is complementary. This RNA representative of the gene, called messenger RNA (mRNA), then passes out of the nucleus into the surrounding body of the cell, the cytoplasm. Here it meets functional units of the cell called ribosomes. These are, in effect, the fabrication shops of the cell.

A ribosome attaches itself at one end of the strand of mRNA and then slowly slides along the strand like a collar. As it does so, the information—the sequence of bases—contained upon the mRNA is

“read” by the ribosome which “instructs” certain molecules of another type of RNA, called transfer RNA (tRNA, which we may liken to towing tractors), to bring up, one by one in the appropriate order, individual molecules of the some 20-odd amino acids present in the cytoplasm. These are linked together in a chain as the ribosome moves along the strand of mRNA, thus forming the particular protein molecule determined by that gene.

In principle this whole process is simple, but in practice it is enormously complicated, involving a whole host of other factors which I will not discuss here. One oversimplified indication of the intricacy of the process is that the chromosome must also contain genes which provide for the synthesis of the amino acids themselves, for the construction of all the other factors, for the building of the ribosome (itself made up of RNA and protein), and for the construction of each of the various tRNAs, one of which is required for each of the some 20-odd different amino acids that go into making up a protein. In addition there are interactive control mechanisms at both the chromosomal and the ribosomal levels.

Now let us go on to our main theme.

#### GENETIC THERAPY FOR DIABETES

As typical of how a particular disability might be treated by genetic means, I wish to focus on the fairly widespread affliction, diabetes, the tendency to which clearly appears to be genetically programmed.

There are in the United States today some 4 million clinical diabetics. Many of these people are kept alive only by repeated frequent injections of the hormone, insulin. It is believed that there are likely several million more subclinical, not clearly recognized, cases with marginal symptoms in the United States.

Without the recurrent injections of insulin, these people would perish. Yet while it keeps diabetics alive, the injection of insulin is not the full equivalent of the normal physiological function; diabetics are known to be more susceptible to infections, to heart and circulatory illnesses and to other afflictions, than are nondiabetics.

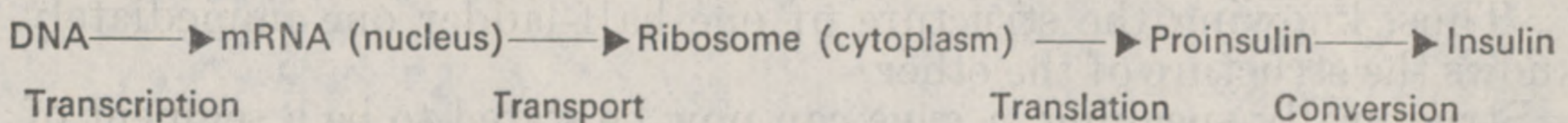


FIGURE 2.—Stages in the expression of the genetic information leading to the synthesis of insulin.

My thesis is that what we might call genetic therapy offers the promise of a much more elegant and indeed more satisfactory physiological solution to this ailment. I would like to consider various possible genetic approaches.

To begin, we must ask: What is the normal process of insulin formation? Insulin is a small protein. That is to say, the insulin molecule is made up of 51 different amino acid subunits which have been linked together. There is recent evidence that indicates strongly that a precursor of insulin, called proinsulin, is first synthesized and this is then chemically modified by an enzyme to form insulin itself.<sup>2</sup>

<sup>2</sup> F. Donald Steiner and Philip Oyer, “The Biosynthesis of Insulin and a Probable Precursor of Insulin by a Human Islet Cell Adenoma,” *Proc. Nat. Acad. Sci.*, Vol. 57, 1967, p. 473-80.

The synthesis of this protein, proinsulin, is accomplished in the usual manner (fig. 2). The hereditary instructions specifying the sequence of amino acids for insulin are encoded in a segment of the DNA in the cell nucleus; these instructions are transcribed into a mRNA molecule which is then transported out of the nucleus to the cytoplasm. There it is translated into protein by the ribosome, with the help of tRNA molecules.

It is well known that normally the synthesis of insulin takes place only in certain cells in the pancreas called the  $\beta$  cells of the Islands of Langerhans. In the diabetic, these cells fail to produce an adequate amount of insulin.

Now it is believed—and there is a good reason for this belief from studies of lower animals<sup>3</sup>—that all the cells of the body, of various types and functions, contain exactly the same chromosomes, which means exactly the same genetic information. (We say that they have the same genome.) Thus, we believe that the genetic instructions specifying the structure of proinsulin are present in all the cells of the body and not only the  $\beta$  cells of the Islands of Langerhans. Evidently, however, these instructions present in other cells are not in use. Either they are not activated or, as it is more fashionable to assume these days, they are repressed. Repression could take place at any of the several stages shown in figure 2.

A typical body cell is called upon to use but a small fraction of its genome. There is good evidence that in a liver or a muscle cell, for example, only at most 5 percent of the DNA is ever transcribed into RNA, so there is repression at the chromosomal level. Further, of that which is transcribed, it is clear that a considerable fraction, perhaps half or more, never reaches the cytoplasm to be translated into the specific proteins. And even if the RNA reaches the cytoplasm there is evidence for specific blocks at the translational level. There are clearly many opportunities for the restriction of expression of the inherited genetic instructions.

Now in the case of insulin we do not know by what means the expression of this gene is limited to a few islands of cells. We do not know at what level the restriction is imposed. Obviously, however, one approach to the problem of diabetes would be to attempt to turn on the synthesis of insulin in another set of cells.

We do know that genes can be turned on by external influence. Hormones do this every day. Under the influence of cortisone, liver cells, for example, initiate the synthesis of quite a variety of enzymes.

We do not know now how we might do this for insulin but we can clearly see the approaches. In fact, of course, just such an activation or derepression for insulin must have occurred at some stage in the development of the embryo to activate—to turn on—the appropriate genes in the  $\beta$  cells of the Islands of Langerhans.

Let us not oversimplify this problem. Obviously, if one wants a new group of cells to synthesize insulin, one must not only activate the gene for proinsulin in those cells, but one must also arrange for its conversion to insulin and for its release from the cells. If we are fortunate, however, these functions might well all come as a genetic package.

<sup>3</sup> John B. Gurdon, "The Transplantation of Living Cell Nuclei," *Advances in Morphogenesis*, Vol. 4, 1964, p. 1-41.

There is a radically different genetic approach that one might alternatively take. Instead of an attempt to lift this profound repression of the expression of the gene for insulin, one might, in principle, supply to a group of cells a wholly new gene or set of genes which would code for the synthesis of insulin and which might well not be subject to the normal pattern of repression.

How might we add, in such a specific manner, to the genetic components of a cell? Leaving aside for the moment the question of where we might obtain the genetic material we wish to add, the tool we would use to implant this genetic material would probably be a virus.

A virus is a very simple "thing" on the margin between life and nonlife. The simpler viruses consist of a relatively short strand of a nucleic acid which has a protein coat around it. A virus may be as short as three genes in length, all that are needed to specify its own reproduction. Its nucleic acid may be either DNA or RNA, and this nucleic acid may be either double-stranded or a single strand only.

A virus can only reproduce itself within a living cell; it requires the use of components of its host. What happens is that the individual virus attaches itself to the wall of the cell it is attacking. Its nucleic acid core is then injected into the cell, leaving the protein coat behind. Inside the cell, the viral nucleic acid takes over the cell's vital processes, and orients these to the reproduction of itself, rather than to the cell's own functions.

Most often, after a few hundred daughter viruses have been produced, complete with protein coat, the cell lyses (bursts open) and the daughter viruses are free to repeat the process on other cells.

The above is the general pattern. But it has variations which are of particular significance here. Our information on these comes from studies on bacteriophages, which are viruses that attack bacteria, and in particular from studies on certain "transducing" bacteriophages.

The bacterial virus P1 contains double-stranded DNA which is several thousand base-pairs in length. When bacterial cells are infected with certain types of P1, the progeny viruses produced are generally identical with the parent virus—except in a little less than 1 percent of the cases. In these exceptional cases the DNA that is given the viral protein coat is not the viral DNA, but instead is a piece of DNA of similar length from the chromosome of the host cell. Different individual ones of these exceptional "mock viruses" will contain different portions of the host chromosome.<sup>4</sup>

By appropriate means these viral particles carrying host DNA can be separated from the normal viruses. These are called transducing particles, for they have the ability to carry genetic material from one cell to another, a process called transduction.

When such transducing particles are added to susceptible bacteria, the DNA inside the virus particle is, in the usual way of bacterial viruses, injected into the cell. But now we have added to the cell, not a destructive virus genome, but a piece of bacterial DNA which may well carry genetic information not present in this particular host. For this piece of DNA to perpetuate itself, however, it must, in

<sup>4</sup>J. Tomizawa and H. Keda, "Transducing Fragments in Generalized Transduction by Phage P1. I: Molecular Origin of Fragments," *J. mol. Biol.*, Vol. 14, 1965, p. 85-109.

general, become incorporated into the host chromosome. It happens that normal bacterial cells have the enzymatic machinery to do this and in the case of the transducing particles of phase P1 there is a good chance—approximately one in ten—that the particular piece of DNA will be incorporated and thus perpetuated.

The second instance of transduction that I wish to describe concerns the temperate bacteriophage lambda. Upon infection with the bacteriophage lambda, the result, in an appreciable percentage of the bacterial cells—it can be the majority—is the physical incorporation either of the viral DNA or one of its descendants into the chromosome of the host.<sup>5</sup> Following this, the virus-like tendencies of this DNA are suppressed. The cell survives and multiplies and the incorporated viral DNA is perpetuated into each daughter cell along with the rest of the bacterial chromosome. Such a virus-carrying cell is said to be a lysogen.

As we shall shortly see, a fact of particular significance is that the point of insertion for the lambda DNA into the host DNA into the host DNA is specific for that particular virus. Various related strains of lambda-type viruses are known, each of which integrates into a different site on the host chromosome.

Now it is possible by appropriate means to induce an activation of this viral DNA in the lysogenic cells—to cause it in effect to remember that it really is a virus: it escapes from the chromosome, multiplies and its hundreds of progeny are released when the bacterium lyses.<sup>6</sup>

Occasionally in such an activation the DNA which is replicated and incorporated into the progeny viruses is not pure viral DNA, but instead a piece of the viral DNA joined together with a piece of the host chromosome adjacent to the site where the parent viral DNA was attached. Viral particles with this mixed DNA can be isolated from the bulk of the progeny. If they are now added to susceptible cells the mixed DNA can still integrate into the host chromosome at the same locus but now adds along with the viral genes a specific piece of DNA from the former host—thereby possibly adding specific new genes into the new host.

In both of these cases, then (P1 and lambda), the net result is the introduction, via a particle normally indistinguishable from a virus, of new genetic material into a host cell. In the first instance the new factors added are random relative to the host genome. In the second, they are factors found at specific sites near the normal region of integration of the virus. In other words, if we knew where on the chromosome a specific gene is located and if we could find a lambda-like virus to attach at that locus, we could pick off that particular gene for transduction on to a host chromosome where that gene might be lacking.

Could a similar transfer be accomplished with a virus in the cells of higher organisms? We have every reason to think yes, and indeed that it does occur.

<sup>5</sup> René Thomas, "Lysogeny," in: L. Crawford and M. Stoker (eds.), *The Molecular Biology of Virus*, 8th Symp. Soc. Gen. Microbiol., 1968, p. 315-42.

<sup>6</sup> B. D. Davis et al., "Lysogeny, Episomes, and Transduction," *Microbiology*, New York, Hoeber Medical Division/Harper & Row, 1967, Chap. 43, p. 1110-11.

There exist a number of viruses that can infect man but are apparently harmless; they cause no injury to the cells they infect. In a fraction of the infected cells the virus becomes established within the cell, attaching to the chromosome (or possibly forming a small secondary body of DNA called an episome) and is faithfully perpetuated into the daughter cells. The viral genetic information is certainly expressed in the original cell and in the daughter cells, for the presence of mRNA derived from such viral DNA can be proved.

Two such benign "passenger" viruses that have been the subject of considerable investigation are simian virus 40 (SV40) and Shope papilloma virus (SPV).

At this point I hope it is clear that technically and literally the stage is set. If we could obtain a virus analogous to SV40 or SPV able to persist in altered cells but carrying the gene for proinsulin, we might indeed be able to provide a genetic alternative to a daily injection of insulin.

But where do we find this virus so propitiously carrying the required gene? Such a virus might exist in nature but I suggest that we are not far away from being able to make it to order. We will have the ability in the not distant future to synthesize a DNA chain capable of coding for proinsulin and carrying the other genes necessary either to integrate the DNA into a chromosome or to maintain it as an episome. And we will then also, if desired, be able to package this *de novo* DNA into an appropriate protein viral coat.

Is this pure fantasy? No, not all. We are advancing steadily toward such a capability. Knowing the genetic code which relates base sequence in DNA to amino acid sequence in protein, we can derive from the known structure of proinsulin the structure of the DNA gene needed to specify this protein.

The completely chemical synthesis of a small gene of specific base sequence has already been accomplished in mid-1970 by Har Gobind Khorana and his colleagues at the University of Wisconsin. The gene in this case, from a yeast chromosome and specifying a transfer RNA, is very small, only 77 base pairs in length. However, the techniques which were developed can surely be applied to the synthesis of much larger genes of DNA.

We would need also to be able to specify and synthesize the gene to code for the enzyme to convert proinsulin to insulin and we would have to provide both of these genes with their appropriate control segments. Then we would need either: (a) to couple these genes to that portion of the DNA of a transducing virus such as SV40 required for integration into the cell DNA (means for performing such joining, *in vitro*, using enzymes which perform similar functions in living cells, have already been partially developed) or (b) to synthesize completely *de novo* the entire DNA of a SV40 virus incorporating the genes required for insulin production in lieu of some of the normal SV40 genes. (After Khorana's achievement of synthesizing a DNA chain 77 base pairs in length, the synthesis of a sequence of 5,000 base pairs—the size of the SV40 chromosome—while certainly difficult is by no means inconceivable.)

Let me point out that the modification of a transducing virus or the complete synthesis of DNA carrying the gene for insulin need only be done once. Once either is available nature provides the means to copy it with the highest fidelity.

It would then be necessary to incorporate this synthetic DNA into a virus protein coat to achieve efficient penetration into cells. Our understanding of the process of viral self-assembly is growing rapidly<sup>7</sup> and with it, but a small step behind, the development of the art of viral assembly in the test tube. Thus the technology needed to apply this radically different approach, the genetic approach, to the solution of a major clinical problem—that of diabetes—is conceptually almost in reach.

#### ANOTHER FORM OF GENETIC THERAPY

The Shope papilloma virus we mentioned earlier presents another interesting illustration of the possibilities of genetic therapy. Not long ago two cases of a disease called arginemia were described. This disease, of genetic origin, is characterized by very high levels of the amino acid, arginine, in the blood. Clinical symptoms of arginemia are severe mental retardation, epilepsy, and various metabolic abnormalities.

It is known that SPV can induce infected cells to synthesize the enzyme, arginase, which decomposes arginine. Experiments have shown that the level of arginine in the blood of rabbits, mice, rats and possibly monkeys is lower after these animals have been infected with this virus. Follow-up studies which were made on some of the numerous investigators who have worked with the Shope virus over the last 40 years, and thus were exposed to possible infection, revealed that about one-half of them carry reduced levels of arginine in their blood although these scientists showed no known symptoms of infection. This effect may persist up to 20 years. It has therefore been proposed that infection with SPV might be used as an effective treatment for arginemia.

As Stanfield Rogers, who has been conducting these studies, states: "This appears to be a clear instance \* \* \* where inoculation with a harmless virus could provide the genetic information in which the patients are deficient."<sup>8</sup>

The analogy is not perfect, yet I feel closely akin to the physicists who pointed out in the 1930's that the principles required for the release of the energy locked in the atomic nucleus were understood. All that we lacked was a practical breakthrough and the requisite technology. Here, too, the principles seem in hand. All that seems really needed is optimism, sustained effort, and support commensurate with the importance of the problem.

The larger and the deeper challenges, those concerned with the designed genetic improvement of man, perhaps fortunately are not yet in our grasp. However, they too are etched clear upon the horizon. We should now begin to prepare their reality and their meaning in the human future—and it is this point I wish to discuss next.

#### THE MAN-DIRECTED EVOLUTION OF MAN

Man has always been doubly tethered to his past: through his genes and through his culture. Until now the cultural tether has been the more elastic. The genetic tether, while undoubtedly changing during

<sup>7</sup> W. Wood and R. S. Edgar, "Building a Bacterial Virus," *Sci. Am.*, vol. 217, 1967, p. 60-75.

<sup>8</sup> Stanfield Rogers, "Skills for Genetic Engineers," *New Scientist*, January 29, 1970, p. 194.

the cultural evolution of man, has been more taut and inflexible. For a very long time we have perforce relied solely upon education as our only means to influence the human spirit and to improve the condition of man. To point out the difficulty of this project, to suggest the possibility of internal limitations to this process of external cultural manipulation has been rightly enough discouraged as a negative, defeatist approach. For there was no alternative.

Today the hidden part of the iceberg, the biological genetic component of human nature, is coming increasingly into view. Fortunately—perhaps inherently, at the same time—our cultural development has proceeded so far that we can soberly envision the means to remould these innate patterns, so long submerged and hidden from conscious knowledge. We can foresee the means to make supple our heredity.

Let me say now that we should not expect unlimited elasticity. The patterns of heredity have their own constraints as do those of culture. But in the dynamic interaction of these two modes of change—which has in the past few millions of years led to man, the creator of culture who is now dependent upon it for his survival and his identity—in this interaction lies the potential for worlds yet undreamt.

I am well aware that there are many who do not regard with optimism this prospect of the designed genetic change of man. Rather they find it deeply alarming and repugnant, and for diverse reasons. It is important and instructive to examine these reasons. If it is a comfort to them, this time is, as I have indicated, not yet upon us. We do not yet have the requisite understanding or means; only the possibility now seems very real.

The most important changes will surely be those concerned with the human mind. About this, we as yet know very little concerning both its genetic basis and its physiological functioning. To comprehend the human brain and to develop the requisite genetic technology may well require the development of a new science equivalent in skill and brilliance and sophistication to the whole of our present science, the product of three centuries of discovery. But that is not a long time in the human experience and I may well overestimate the task.

In part, the alarm expressed by many strikes me as an understandable response to profound novelty. We have, over time, developed a variety of institutions to change—to improve—our cultural inheritance: books and the printing press, our educational process, religious and secular, our scientific endeavour. I expect that many of these would have seemed absurd, alien and even dangerous to a primitive, had someone endeavoured to propose a defined program for their development 5,000 years ago. These institutions were developed gradually, haltingly, painfully over the centuries. By simple criteria such as survival they are considered to be advances and have become integral components of our civilization.

Because until now it has simply not been possible, we have not developed institutions to change, improve, our biological inheritance. As we now set out to do this no doubt what we may conceive will seem at first absurd, alien, and dangerous. But in the end we may come to see the improvement of our biological inheritance to be as natural and as important as the improvement of our cultural inheritance. Indeed, we might see the two as essential complements, each of the other.

Another voice of alarm is heard from those who believe—with much evidence—that because we are human we should expect to err, and who fear that if we unleash forces beyond human scale, even a minute error may prove to be beyond remedy. This caution we should indeed bear in mind.

We must so blend the gifts of foresight and restraint that we do not do that which we cannot undo. For the stake here is the entire continuity of evolution. Yet, to quote Alfred Whitehead: "Panic of error is the death of progress and love of truth is its safeguard."

There is a different concern, that if one begins to change the nature of man he will be, in a profound sense, less human. This could well be. But I cannot celebrate all things human, for there is in us yet too much of our clawing past. Would a man be less human if he never knew hate or rage or envy or terror? Perhaps: in a strange sense he might be less human but more humane.

Would our society be less human if it lacked the crippled, the mentally defective, the emotionally warped or frozen? Perhaps: it would be less varied, less colorful, but also less sordid and harsh, less cruel and pathetic. Men could be less the victims of an ironical fate and more the charterers of their individual destinies.

It is true that such a man could not comprehend Shakespeare; for him, the Bible would be written in an alien tongue. And it must be our concern that any such changes be gradual, that such persons not feel too rootless, too foreign and remote from all that has gone before, as indeed we do from the other primates.

There are also those who recoil at another prospect; they hear herein the death knell of the doctrine of blame, the dissolution of individual responsibility. To my mind this is hyperbole, though it is an overdue recognition of the logical consequences of an increasingly interdependent society.

We are approaching that point in time at which the bonds linking the individual to society, which have become progressively ever firmer, may become stronger than those which sustain his personal integrity, when even his inner nature will have become the consequence of a social decision.

I do not think this need exclude individual responsibility. There is the option that the character of that social decision can yet be such as to strengthen and sustain personal integrity, although we need to recognize and clearly acknowledge this objective.

We must recognize that we are coming to live increasingly in a world of our own design. Unless we choose otherwise this could be a world in which the unexpected is only a miscalculation and wonder is reserved for the very young, a world in which as we remould our planet into a projection of our inner selves, we begin to close in upon ourselves—for when all is man-made where shall we gain new inspiration?

The only exit from this cycle will be to change man himself, to escape the tyranny of genetically patterned development, to enlarge his competence, to permit him to acquire new potentials and envision new horizons, to sustain his individual integrity by expanding his capacities to cope with complex and varied circumstances.

We have always relied upon a few individuals, rarely gifted and at the outer limits of human capability, to lead us out of the brute past.

In science we discovered a magnificent tool to corroborate and cumulate the efforts of these few over many generations. They have led the rest of us out of darkness by example and persuasion and promise. It has been, in a deep sense, a thin margin.

Now we may reasonably soon achieve something new. We may increase the number of those who can so lead and we may increase the adaptability of all to follow into a higher plane.

We need to do so. For an unanticipated and perilous byproduct of our progress has been the growing fracture of our culture. As we increase knowledge and refinement in every field of endeavor, the time and effort required to master each discipline has grown to divide us into distinct, noncommunicating cultural species. To reintegrate men we need to enhance, genetically, our capacities relative to our opportunities—to augment the ability of each to comprehend the other.

In so doing, however, I hope we will always bear in mind the distinctive value of our individual humanity. As human beings we should aim to create a new mode of cooperative organization, one in which anarchic interaction is restricted not by rigid inherited structure and stereotyped response but by conscious understanding, by anticipation, by wisdom and grace and compassion—a social order which seeks to maintain and to augment its capacity for creative innovation tempered by simple humanity.

The aims of genetic technology should be to enhance the capacities of each individual to comprehend and to cope freely with the complexities of interactive society, to enlarge the internal margin of humanity, to transcend our conceptual limitations.

I would offer five maxims for the future genetic technology; they are couched in borrowed terms:

Do not eliminate all of chance and novelty—for that is the way to extinction.

Do not create defined subtypes—for that is the way of the ant.

Do not chill all passion—for that is the way of the drone.

Do not diminish the heart—for that is the way of the robot.

Do not erase the ego—for that is the way of the slave.

Paul Tillich wrote: "Man becomes truly human only at the moment of decision." We should aim always to enlarge his opportunities and capacities for decision.

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## SPECIAL ARTICLE

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### B. ETHICAL ASPECTS OF GENETIC CONTROLS\*

#### DESIGNED GENETIC CHANGES IN MAN

(By Joseph Fletcher, B.D., S.T.D.)

#### ABSTRACT

Genetic medicine and manipulation are challenged on ethical grounds. The attack includes a condemnation of sacrifice even of a zygote as a form of abortion, abortion being held to be (as such) immoral. This means that embryology,

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fetology and all forms of laboratory reproduction are immoral—that physicians and scientists are murderers. The ethical issue is between those who determine what is right or wrong by consequences, as most people in medicine and society do, and those who (like the moralists who condemn all abortion, no matter how early) decide what is right on a priori grounds, often metarational or religious. On the basis of consequences neither abortion nor genetic control can be condemned. It would depend on the case and the values we seek, is humanness something given in a conceptus, or something that develops in it? Are fetal “rights” more important than human needs?

The essential difference between science and ethics is that science is descriptive and ethics is prescriptive. Science deals with what is, in the indicative mood. Ethics deals with what ought to be, in the imperative mood. Scientific theories and statements depend for their validity upon verification (are they correct?); ethical theories and statements depend upon justification (do they conduce to the good?).

The ethical question, then, is whether we can justify designed genetic changes in man, for the sake of both therapeutic and nontherapeutic benefits. We are able to carry out both negative or corrective eugenics—for example, to obviate gross chromosomal disorders—and positive or constructive eugenics—for example, to specialize an individual’s genetic constitution for a special vocation. Like all other problems in ethical analysis, the morality of genetic intervention and engineering comes down to the question of means and ends, or of acts and consequences. Can we justify the goals and the methods of genetic engineering?

Unlike many other problems, however, in this one both the means and the ends are either challenged or actually condemned. This makes it a thornier ethical issue than most others. In bacteriologic warfare, for example, the means or weaponry is sometimes opposed even by those who may morally support a war’s goal—that is, to subjugate an enemy. In education, to take a different kind of case, to have as the end or goal establishing an Orwellian group-think in the populace would be rejected by most of us, even though the means—various mass media—are regarded as morally licit and ordinarily a good thing.

Those who wish to defend or encourage genetic controls are therefore put in the position not only of having to justify such means in embryologic and genetic research as the in-vitro fertilization (conception) of human organisms or the vegetative (mitotic) reproduction of human embryos by cloning, but also of having to justify the end—that is, contrived human beings psychophysically improved by biologic design and control.

The relation of means to ends is central to ethical analysis. Does a morally desirable end ever justify a bad means, on the principle of proportionate good? Could a good means ever justify an evil end or consequences—again on the principle of proportionate good? I would answer Yes to both questions, for reasons that will appear as we proceed. The phrase “good end,” I shall contend means only that the end or consequence sought is ordinarily or commonly good, not absolutely good regardless of circumstances. In the same way the phrase “good means” can mean only that this or that method of getting to the goal desired, the act, is ordinarily or commonly right, not absolutely or always right in and of itself. Furthermore, it is obvious that our values, the various elements we hold to make up goodness, must also be identified and declared in this inquiry. Altogether, this poses a complex but important bundle of questions for conscientious people.

Moral judgments differ. Some people fear new and unexplored risks, as we can see (for example) in the debate over construction of nuclear powerplants. They prefer to forget risk-benefit calculations; they like to stay on the safe side. Others distrust any enlargement of potential powers that might give some of us some advantage over others. We are all familiar with C. S. Lewis' observation that each new power won by man is a power over man as well. Certainly, genetic design would be such a power; even though its medical aim were only to gain control over the basic "stuff" of our human constitution it could no doubt also be turned into an instrument of political power, with or without the reinforcement of Huxley's imaginary "soma." Is it possible, some wonder, echoing Henry David Thoreau, that men have become the tools of their tools?

Nobel laureate George Beadle's opinion is that "Man knows enough but is not wise enough to make man" (1). Over against his way of looking at it a Canadian biologist, N. J. Berill, says, "Sooner or later one human society or another will launch out on this adventure, whether the rest of mankind approves or not. If this happens, and a superior race emerges with greater intelligence and longer lives, how will these people look upon those who are lagging behind? One thing is certain: they, not we, will be the heirs to the future, and they will assume control" (2).

Among religionists, Canon Michael Hamilton, of the National Cathedral in Washington, approves of genetic engineering, when and if it is aimed at the personal improvement of humans (3). At the same time a Jesuit theologian, Richard McCormick, condemns it because, he believes, only monogamously married heterosexual reproduction is morally licit (4). Wearing his philosopher's hat, J. B. S. Haldane votes for genetic design (5), but putting on the same hat, another biologist, Theodosius Dobshansky, votes against it (6). Disagreement is obviously at work at all levels and in all intellectual camps, from the simplest people to scientific peers.

A careful approach to the issue will avoid what I call the capacity-fallacy—that is, the notion that because we can do something, such as genetic control, we ought to. It does not follow that because we could, we should. There is an ethical parallel in the necessity-fallacy, the assumption by some culture analysts that because we can do something, we will. Those who are fatalists—a visceral or noncephalic condition that is fairly widespread among us—naturally do not bother to ask policy questions.

Leaving aside technical philosophical conventions, let me suggest that when we tackle right-wrong or good-evil or desirable-undesirable questions there are fundamentally two alternative lines of approach. The first one supposes that whether any act or course of action is right or wrong depends on its consequences. The second approach supposes that our actions are right or wrong according to whether they comply with general moral principles or prefabricated rules of conduct. Kant's formula, "It is always wrong to treat people as means and not as ends," would be an example of decision by moral rules, or the pacifist's use of the fifth of the Ten Commandments, "Thou shalt not kill." The first approach is consequentialist; the second is a priori.

This is the rock-bottom issue, and it is also (I want to suggest) the definitive question in the ethical analysis of genetic control. Are we to reason from general propositions and universals to normative decisions, or are we to reason from empirical data, variable situations and human values to normative decisions? Which? One or the other.

Until modern times the most common form of a priori ethics was religious morality. It usually held in advance of any concrete or actual problem of conscience that certain kinds of acts, such as lying and stealing and fornicating, are always wrong intrinsically, in and of themselves, as such. Their inherent wrongness was believed by faith and by metaphysical opinion to be a matter of "natural" moral law or of divine revelation. They were always negatives, never affirmatives—prohibitions, not obligations. Such "moral laws" were presumably known to the moral agent—the actor or decisionmaker—through inner guidance or intuition, or by spirit guidance from outside, or by means of some more objective special revelation, like scriptures. In any case, right and wrong were determined by a religious or metaphysical or nonempirical kind of cognition. There is still a widespread disposition to take an ethical posture of this kind, even though it is often unconscious. It is metarational ethics.

Nonconsequentialists would say, therefore, that therapeutic or corrective goals are not enough to justify *in vitro* fertilization, positive eugenics or designed genetic changes, no matter how desirable they might be. It was this kind of ethics that Daniele Petrucci ran into several years ago in Bologna because of his experiments with artificial fertilization and cell divisions at preblastocyst stages. The Church forced him to stop, in a kind of modern Galileo episode.

The basic moral law here was the religious belief that "only God can make a tree" and only God should make a man. On this basis it would be wrong to use artificial fertilization, insemination or innovulation, or single cell replication in ectogenesis. And this "law" of the divine monopoly is also opposed to any human control of sexually produced conceptuses. In the same way it is believed that fertilization results directly in a "human" being or a "nascent" human being, so that the laboratory sacrifice of such zygotes, or the use of a prostaglandin, being abortifacient, would be intrinsically wrong as such—that is, "murder."

Good consequences could not, to the priori moralist, justify such acts or procedures since they are wrong as means, and the a priorist contends that "the end does not justify the means." The principle of proportionate good, or a balance of gains over costs, could not in their ethics make genetic intervention by laboratory reproduction morally permissible. Consequences, as they see it, do not decide what is right. At a recent discussion at Airlie House, Dr. Leon Kass, a molecular biologist working for the National Research Council, put the a priori position succinctly. "Morally," he said, "it is insufficient that your motives are good, that your ends are unobjectionable, that you do the procedure "lovingly" and even that you may be lucky in the result: you will be engaging in an unethical experiment upon a human subject." (7) This is also the opinion of Paul Ramsey, a Protestant moralist who, like Father McCormick, believes that such procedures

as artificial insemination from a donor, artificial inoovulation, cloning, and other forms of asexual reproduction are wrong—wrong because morally licit reproduction must be done heterosexually by human intercourse within the context of marriage and the family. (8).

However, some a priori moral principles are not based on metaphysical grounds. One school of utilitarians, called "rule utilitarians," make moral choices on the basis of generalizations reached empirically or clinically. They might conclude that in the expectable results of laboratory reproduction and genetic engineering, the good would be outweighed by the evil, or that the attendant risks are unknown or too great, and that therefore such procedures should be disapproved as a class or category.

Here, there is no attempt to assign an intrinsic value or disvalue; it is strictly an extrinsic appraisal. Their reason for resorting to categorical principles is usually like G. E. Moore's: that they are unwilling to trust their own judgment in situations that are apparently exceptions to the general rule. They therefore simply "rule out" some class actions (such as genetic designing) universally and categorically. Outside some theological and philosophical circles, most of the opposition to designed genetic changes in man, or even to genetic intervention for therapeutic purposes, is based on rule-utilitarianism.

In this connection, by the way, it is only fair to point out that all religionists are not a prioristic: for example, Prof. James Gustafson, of the Yale Divinity School, has asked if biomedical changes in man are intrinsically wrong and answered in the negative, but he then added that if its consequences were antihuman it would for that reason be wrong after all. (9) (Later, we shall have cause to return to this matter of the human and nonhuman.)

The more commonly held ethical approach is a different modality, a pragmatic one—sometimes sneered at by a priorists and called a "mere morality of goals." This ethics is my own, and I believe it is implicit in the ethics of all biomedical research and development as well as in medical care. We reason from the data of each actual case or problem and then choose the course that offers an optimum or maximum of desirable consequences.

On this basis we cannot reason deductively from a priori or predetermined rules about the moral justifiability of whole classes of acts, such as the *in vitro* fertilization of gametes and the experimental sacrifice of test zygotes, or the cloning of animal and human organisms. We agree with Jeremy Bentham: "If any act can with propriety be termed pernicious, it must be so by virtue of some events which are its consequences \* \* \* no act, strictly speaking, can be evil in itself" (10).

For those whom we might call situational or clinical consequentialists results are what counts, and results are good when they contribute to human well-being. On that basis the real issue ethically is whether genetic change in man will, in its foreseeable or predictable results, add to or take away from human welfare. We do not act by a priori categorical rules nor by dogmatic principles, such as the religious-faith proposition that genetic intervention is forbidden to human initiative or the metaphysical claim that every individual has an inalienable right to a unique genotype—presumably according to however chance and the general gene pool might happen to constitute it.

For consequentialists, making decisions empirically is the problem. The question becomes, "When would it be right, and when would it be wrong?"

#### GENETIC ENGINEERING MUST BE SELECTIVE

What, then, might be a situation in which constructive or positive eugenics would be justified because the good to be gained—the proportionate good—would be great enough? Another way of putting it is, "When would its utility justify it?" My ability to futurize, as they say nowadays, is very limited: I am not much of a seer or forecaster, and I feel uncomfortable attempting to predict shocks of the future in long time spans. But we have to try, even though it raises our anxiety level. We owe a great obligation to the future and to our descendants, and it would be irresponsible to repudiate the problem of genetic control by either a blanket condemnation or an uncritical endorsement. As Kierkegaard said, "To venture causes anxiety, but not to venture is to lose oneself."

Take cloning of humans, for example, as a form of genetic engineering. Although Joshua Lederberg, another Nobelist in microbiology, may be correct when he says that cloning is "merely speculative" until more experimental work with animals is done, it is still possible that such science-fiction scenarios can help value analysis and ethical examination. Diderot, G. B. Shaw, H. G. Wells, Huxley, and Lederberg himself have all foretold genetic engineering. As crystal-ball gazers they have until recently been like Priam's daughter, Cassandra, doubted and pooh-poohed. But now things are different. Now not only the doomsday people but the tut-tut reactors are having a harder time.

And yet, just because cloning is defensible in asparagus or carrot growing, it does not follow that it is all right in human baby making. I respect the ethics of scientists, which is primarily a love for and search for the facts, but some scientists seem to have an almost blind faith that somehow the facts will be used to good purposes, not misused for evil. But this is too complacent as we face the wide margin of personal and social dangers in biomedical research and practice. Therefore, whether and when genetic control could be right would depend on the situation. Let's look at a few cases, both therapeutic and eugenic.

There might be a need in the social order at large for one or more people specially constituted genetically to survive long periods outside bathyspheres at great marine depths, or outside space capsules at great heights. Control of a child's sex by cloning, to avoid any one of 50 sex-linked genetic diseases, or to meet a family's survival need, might be justifiable. I would vote for laboratory fertilization from donors to give a child to an infertile pair of spouses.

It is entirely possible, given our present increasing pollution of the human gene pool through uncontrolled sexual reproduction, that we might have to replicate healthy people to compensate for the spread of genetic diseases and to elevate the plus factors available in ordinary reproduction. It could easily come about that overpopulation would force us to put a stop to general fecundity, and then, to avoid discrimination, to resort to laboratory reproduction from unidentified cell sources. If we had "cell banks" in which the tissue of a species of

wild life in danger of extinction could be stored for replication, we could do the same for the sake of endangered humans, such as the Hairy Ainu in northern Japan or certain strains of Romani gypsies.

If the greatest good of the greatest number (i.e., the social good) were served by it, it would be justifiable not only to specialize the capacities of people by cloning or by constructive genetic engineering, but also to bioengineer or biodesign parahumans or "modified men"—as chimeras (part animal) or cyborg-androids (part prosthetes). I would vote for cloning top-grade soldiers and scientists, or for supplying them through other genetic means, if they were needed to offset an elitist or tyrannical power plot by other cloners—a truly science-fiction situation, but imaginable. I suspect I would favor making and using man-machine hybrids rather than genetically designed people for dull, unrewarding or dangerous roles needed nonetheless for the community's welfare—perhaps the testing of suspected pollution areas or the investigation of threatening volcanos or snow-slides.

Ours is a Promethean situation. We cannot clearly see what the promises and the dangers are. Both are there, in the biomedical potential. Much of the scare-mongering by whole-hog or a priori opponents of genetic control link it with tyranny. This is false and misleading. Their propaganda line supposes, for one thing, that a cloned person would be a "carbon copy" of his single-cell parent because the genotype is repeated, as if such genetically designed individuals would have no individuating personal histories or variable environments. Personalities are not shaped alone by genotypes.

Furthermore, they presume that society will be a dictatorship and that such designed or cloned people would not be allowed to marry or reproduce from the social gene pool, nor be free to choose roles and functions other than the ones for which they had a special constitutional capability. But is this realistic? Is it not, actually, a mood or attitudinal posture rather than a rational or problematic view of the question?

Dr. Lederberg has pointed out that although the scenario of the Brave New World has been widely advertised, emphasizing that a slave state could and probably would use genetic control, still "it could not be so without having instituted slavery in the first place." He adds, "It is indeed true that I might fear the control of my behavior through electrical impulses directed into my brain but . . . I do not accept the implantation of the electrodes except at the point of a gun: the gun is the problem." (11) I agree. The danger of tyranny is a real danger. But genetic controls do not lead to dictatorship—if there is any cause-and-effect relation between them it is the other way around—the reverse. People who appeal to Brave New World and 1984 and Fahrenheit 451 forget this, that the tyranny is set up first and then genetic controls are employed. The problem of misuse is political, not biological.

#### REPRODUCTION IN THE LABORATORY

The possibility of an ethical justification of genetic control, such as I have indicated, leads at once to the question of an ethical defense of its essential prerequisite—embryologic and genetic research. As

I said at the outset, there are serious challenges not only to the end being sought (control) but also to the morality of the means—in vitro fertilizations, benchmade zygotes and embryos, and the entailed practice of their sacrifice in the course of investigation. If we can justify the end, can we justify the means? Does the end justify the means in this particular case? My answer is a positive, "Yes".

I can see only one possible objection to such research, given a humanistic and situational ethics of the sort I have explained. That objection would be that fertilizations or cloning result directly and instantly in human beings, or in creatures with nascent or proto-human status. Let me say at once that I do not believe this to be true. And that is what such a proposition calls for—belief in a faith assertion, a declaration or confession of faith. It is not in the order of either scientific or rational statements to say that such early cell tissue is human (except in the sense of the biologic specification): it is an a priori metarational opinion. It effectively excludes from its ethics all nonbelievers.

For example, a Catholic obstetrician in Washington, D.C., has complained that it is "arbitrary" to start regarding a fetus as human at the 20th week or at "viability," and yet the physician himself insists on the even more arbitrary religious doctrine that a fertilized ovum before implantation is human. (12) Granted that it is difficult to check off any specific point on the gestational continuum as the start of a human being, it is obvious that there is much more to be said for viability as that point than for fertilization.

Those who believe such things may be correct. There is no way to know whether they are or not. It follows for them deductively that abortion is wrong in any of its manifold forms, before or after nidation. It would also follow that the experimental sacrifice of zygotes and blastular embryos in the research process is the destruction of innocent human life or the "killing of unborn babies."

This rhetoric is again an instance of how a priori ethics reasons syllogistically from metaphysical and metarational premises to a normative conclusion, rather than consequentially. All the good results in the world, immediately or potentially, could not (they argue) justify what is wrong—in this case "homicide." Indeed, if anybody really believes that a zygote is a human being he or she ought not to terminate a pregnancy or engage in embryologic research, not only for the sake of ethical consistency but for the sake of their own mental and emotional balance.

But most of us do not make that faith assertion. This is precisely and basically what is at stake in the national debate about abortion laws—the fact that they rest on grounds of a private, personal religious conviction and should not therefore be established by government in violation of the Constitution's first amendment. Obstetricians and gynecologists do not believe this doctrine, nor do surgeons, nor do fetologists, nor do embryologists and geneticists—except for an atypical minority involved in certain religious groups.

There are, be it noted, additional auxiliary arguments used sometimes against the research sacrifice of embryos and other fetal life, such as the claim that "it tends to lower respect for human life." But

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References at end of article.

this begs the question and is not really very convincing as a consequentialist argument (which it is) and is very likely in any case to be a cover-up for the notion that fallopian and uterine cell matter is human. There is also a "feeling" in some discussants that a conceptus somehow has a "right to be born." They would be better advised to follow the reasoning of our common and statutory law, which rejects any idea of "unborn babies" and restricts the status of "baby" to the neonate, denying that any rights at all may be assigned to a fetus.

Nevertheless, these objections to laboratory reproduction uncover two further points I feel obliged to establish. Both points are meta-ethical in nature or at least prenormative. The first has to do with the idea of "humanness" and the second has to do with the notion of "rights."

What does it mean to say, as Dr. Kass does, that "the laboratory reproduction of human beings is no longer human procreation"? (7) (Indeed, can he reasonably charge that laboratory reproduction is nonhuman and still call its products "human beings"?) Man is a maker and a selector and a designer, and the more rationally contrived and deliberate anything is, the more human it is. Any attempt to set up an antinomy between natural and biologic reproduction, on the one hand, and artificial or designed reproduction, on the other, is absurd. The real difference is between accidental or random reproduction and rationally willed or chosen reproduction. In either case it will be biologic—according to the nature of the biologic process. If it is "unnatural" it can be so only in the sense that all medicine is.

It seems to me that laboratory reproduction is radically human compared to conception by ordinary heterosexual intercourse. It is willed, chosen, purposed and controlled, and surely these are among the traits that distinguish *homo sapiens* from others in the animal genus, from the primates down. Coital reproduction is, therefore, less human than laboratory reproduction—more fun, to be sure, but with our separation of babymaking from lovemaking, both become more human because they are matters of choice, and not chance. This is, of course, essentially the case for planned parenthood. I cannot see how either humanity or morality are served by genetic roulette.

#### WHAT IS HUMAN?

The fact is that most of our discourse about the ethics of biomedical innovation is a semantic swamp, because what we mean by "human" and ergo by "humanistic" usually remains vague and poorly defined. The question "What is it to be human?" is, however, no longer just an academic exercise for philosophers. Physicians and nurses, as well as geneticists and laboratory technicians, face it every day thousands of times. For them it is literally a life-and-death practical question. It arises in utero or in vitro when sacrifices are indicated, and it arises in terminus when decisions have to be made whether to go on prolonging a patient's dying. When does a fetus become human (the better term is "personal"), when is a dying patient no longer so?

Let me suggest a conceptual approach that might be adopted. In the light of medical proposals to redefine death in terms of irreversible coma or a loss of the higher brain function (what some call cerebral)—it might be due to a massive hemorrhage, or a neoplasm, or

a trauma—if such an ex-cerebral patient is no longer alive in any human sense or personal sense, would it not follow that a precerebral embryo or fetus is not yet alive in any human and personal sense? This would, of course, obviate any further use of such question-begging rhetoric as “killing unborn babies.”

In any case, what is called for here, for consequentialists, is a quality-of-life ethics instead of the sanctity-of-life ethics in the classical Western tradition. The metarational premise or a priori that mere life or biologic process is sacrosanct is not only neither verifiable nor falsifiable; by logical inference it is inconsistent with empirical and humanistic medicine, as well as opposed to genetic and embryologic investigation.

The uncomfortable truth is that we have not yet put our heads together in an interdisciplinary way to see if we can find some “common ground” factors and operational terms for such synthetic concepts as “human” and “personal.” Some moralists—for example, Gustafson (9)—doubt if a consensus on “humanness” is possible, but it is worth a try. This may well be the most searching and fundamental problem that faces not only ethicists but society as a whole.

It is already very late. It is urgent that scientists, philosophers, sociologists, lawyers, and theologians make the attempt, especially if nondoctrinaire auspices can be found. What makes a creature human? A minimum of cerebrocortical function? Self-awareness and self-control? Memory? A sense of futurity, of time? A capacity for interpersonal relationship? Communication? Love? A minimum IQ? Could we add a desire to live? What else? And in what order would we rank them as priorities?

Surely Senator Mondale was on the right track in 1968 when he tried to persuade Congress to propose a National Commission on Health, Science, and Society. It was obstructed by people in research medicine objecting to any outside “interference.” Another effort, Senate Resolution 98, was also sidetracked, in the 91st Congress of 1969. Senator Mondale promises to try again in 1971. The alternative to such a thoughtful review of the implications of biomedical pioneering is apt to be hasty, unconsidered legislation. There is a palpable danger of a new Luddism, biologic this time instead of industrial. Little as we should like to be manipulated by what Gerald Leach has called the biocrats (13), neither do we want to be paralyzed by know-nothingism.

Science deals with the possible and the probable, but ethics deals with the preferable—and it is at this level of analysis that the issue of designed genetic changes in man has at last brought us. We cannot any longer sweep it under the rug.

#### NEEDS FIRST, NOT RIGHTS

My second closing point has to do with what we mean by rights. Reactionaries cannot, of course, “prove” that reproduction is ethical only when it is done heterosexually within the monogamous marriage bond, or that any one set of values or any one preferential order is the correct one, or that particular “rights” alleged by this group or that are sacrosanct. None of them are. For example, we cannot establish a

supposed "right to be born," to say nothing of what one theologian has called a right to be born with a unique genotype (14). (By this, of course, he can only mean the accidental genotype resulting from random or so-called natural conception, and even so, identical twins can and do occur in nature.) All alleged "rights" are at best imperfect and relative. But what is there, then, to appeal to, to validate our humanistic concerns and our person-centered values?

My answer is: needs. Needs are the moral stabilizers, not rights. The legalistic temper gives first place to right, but the humanistic temper puts needs in the driver's seat. If human rights conflict with human needs, let needs prevail. If medical care can use genetic controls preventively to protect people from disease or deformity, or to ameliorate such things, then let so-called rights to be born step aside. If research with embryos and fetal tissue is needed to give us the means to cure and prevent the tragedies of "unique genotypes," even though it involves the sacrifice of some conceptuses, then let rights take a back seat.

Rights are nothing but a formal recognition by society of certain human needs, and as needs change with changing conditions so right should change too. The right to conceive and bear children has to stop short of knowingly making cripple children—and genetics gives us that knowledge—just as the rights of parents have had to bow to required schooling and the rights of voluntary association have had to bow, in public services, to the human need to be respected regardless of ethnic and racial differences. It is human need that validates rights, not the other way around. I for one am not primarily concerned about any claimed rights to live or to die; I am first of all concerned about human needs, and whether they are met by life or by death will depend on the situation.

To speak of "needs" is to speak of human values. How shall we identify and rank-order them? Here, again, we have to have across-the-board cultural consultation. I agree with Michael Baram, of MIT, who says:

I do not think scientific peer groups presently have the objectivity or capability to function as coherent and humane social controls. The members of a peer group share the narrow confines of their discipline, and individual success is measured by the degree to which one plunges more deeply into and more narrowly draws the bounds of his research. There are no peer group rewards for activities or perceptions that extend beyond the discipline or relate it to social problems. Members are therefore neither motivated nor trained to relate their peer group activity to broader social problems.

Self-enclosed peer groups cannot be entrusted with self-control \* \* \* because our educational system does not foster ethical and interdisciplinary values in professional training.

(15)

Owing to the work of microbiologists and embryologists we are already able to produce babies born from parents who are separated by space or even by death; women are already able to nourish and

gestate other women's children; one man can "father" thousands of children; virgin births or parthenogenesis (for that is what cloning is) are likely soon to be feasible; by genetic intervention we can shape babies, rather than only from the simple seed of our loins; artificial wombs and placentas are projected by biochemists and pharmacologists. All this means that we are going to have to change or alter our old ideas about who or what a father is, or a mother, or a family. Francis Crick, codescriber of DNA, and others are quite right to say that all this is going to destroy to some extent our traditional grounds for ethical beliefs.

But whatsoever new mental images take shape, within new reality situations, as long as they are tailored to a loving concern for human beings we need not be afraid. Fear is at the bottom of this debate—some of it the conventional wisdom's fear of change, some of it a fear of science, and some of it fear of freedom's power and creative control. It is perhaps, the fear of fear itself that makes for a lot of hang-ups and copouts. But however, that may be, the historic moral order has always presupposed heterosexual coital conception as necessary for the continuance of life, and now that is no longer the case. The familiar phrase "the facts of life" is an archaism.

I agree with Roger Shinn that in the sequence or progression from aspirin to insulin to artificial kidneys to brain surgery to genetic engineering there is no point at which we can "change from a clear yes to an absolute no," even though there is a mounting difference in the complexity of the ethical issues posed (16). We cannot accept the "invisible hand" of blind natural chance or random nature in genetics any more than we could old Professor Jevon's theory of feast and famine in 19th-century laissez-faire economics, based on sunspots and tidal movements. To be men we must be in control. That is the first and last ethical word. For when there is no choice there is no possibility of ethical action. Whatever we are compelled to do is amoral.

The moral philosopher, sensitive to social ethics, can only echo what the biologist Robert Sinsheimer has said: "As the discoveries accumulate, as new means of biological intervention arise, we can envision such possibilities as the almost indefinite prolongation of life for at least a few, the deliberate predetermination of sex, or the design of human genetic change for varied purposes. With these will come the necessity for multiple social decisions of the most profound consequence" (17).

The pressure of social decisionmaking is now forcing us to dig deeper than the technical hardware sciences; we now have to grapple with the personal and human software sciences—especially biology and the crossroads it reveals to us, just ahead.

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## C. PROSPECT FOR GENETIC INTERVENTION IN MAN\*

CONTROL OF POLYGENIC BEHAVIORAL TRAITS IS MUCH LESS LIKELY THAN  
CURE OF MONOGENIC DISEASES

(By Bernard D. Davis\*\*)

Extrapolating from the spectacular successes of molecular genetics, a number of essays and symposia (1) have considered the feasibility of various forms of genetic intervention (2) in man. Some of these statements, and many articles in the popular press, have tended toward exuberant, Promethean predictions of unlimited control and have led the public to expect the blue-printing of human personalities. Most geneticists, however, have had more restrained second thoughts.

Nevertheless, recent alarms about this problem have caused wide public concern, and understandably so. With nuclear energy threatening global catastrophe and with so many other technological advances visibly damaging the quality of life, who would wish to have scientists tampering with man's inner nature? Indeed, fear of such manipulation may arouse even more anxiety than fear of death. The mass media have accordingly welcomed sensational pronouncements about the dangers.

While such dangers clearly exist, it also seems clear that some scientists have dramatized them (3) in order to help persuade the public of the need for radical changes in our form of government (4). But however laudable the desire to improve our social structure, and however urgent the need to improve our protection against harmful uses of science and technology, exaggeration of the dangers from genetics will inevitably contribute to an already distorted public view, which increasingly blames science for our problems and ignores its contributions to our welfare. Indeed, irresponsible hyperbole on the genetic issue has already influenced the funding of research (5). It therefore seems important to try to assess objectively the prospects for modifying the pattern of genes of a human being by various means. But let us first note two genetic principles that must be taken into account.

## RELEVANT GENETIC PRINCIPLES

*Polygenic traits and behavioral genetics.*—The recognition of a gene, in classical genetics, depends on following the distribution of two alternative forms (alleles) from parents to progeny. In the early years of genetics, after the rediscovery of Mendel's laws in 1900, this analysis was possible only for those genes that exerted an all-or-none control over a corresponding monogenic trait—for example, flower color, eye color, or a hereditary disease such as hemophilia. The study of such genes has continued to dominate genetics. However, monogenic traits constitute a small, special class. Most traits are polygenic: that is, they depend on multiple genes, and so they vary continuously rather than in an all-or-none manner. Moreover, each gene itself is polymorphic—that is, it is capable of existing, as a result of mutation, in a variety of different forms (alleles); and though the protein products of these alleles differ only slightly in structure, they often differ markedly in activity.

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For our purpose it is especially pertinent that the most interesting human traits—relating to intelligence, temperament, and physical structure—are highly polygenic. Indeed, man undoubtedly has hundreds of thousands of genes for polygenic traits, compared with a few hundred recognizable through their control over monogenic traits. However, the study of polygenic inheritance is still primitive; and the difference from monogenic inheritance has received little public attention. Education on the distinction between monogenic and polygenic inheritance is clearly important if the public is to distinguish between realistic and wild projections for future developments in genetic intervention in man.

*Interaction of heredity and environment.*—The study of polygenic inheritance is difficult in part because it requires statistical analysis of the consequences of reassortment, among the progeny, of many interacting genes. In addition, even a full set of relevant genes does not fixedly determine the corresponding trait. Rather, most genes contribute to determining a range of potential for a given trait in an individual, while his past and present environments determine his phenotype (that is, his actual state) within that range. At a molecular level the explanation is now clear; the structure of a gene determines the structure of a corresponding protein, while the interaction of the gene with subtle regulatory mechanisms, which respond to stimuli from the environment, determines the amount of the protein made. Hence, the ancient formulation of the question of heredity versus environment (nature versus nurture) in qualitative terms has presented a false dichotomy, which has led only to sterile arguments.

#### POSSIBILITIES IN GENETIC MANIPULATION

*Somatic cell alteration.*—Bacterial genes can already be isolated (6) and synthesized (7); and while the isolation of human genes still appears to be a formidable task, it may also be accomplished quite soon. We would then be able to synthesize and to modify human genes in the test tube. However, the incorporation of externally supplied genes into human cells is another matter. For while small blocs of genes can be introduced in bacteria, either as naked DNA (transformation) or as part of a nonlethal virus (transduction), we have no basis for estimating how hard it will be to overcome the obstacles to applying these methods to human cells. And if it does become possible to incorporate a desired gene into some cells, in the intact body, incorporation into all the cells that could profit thereby may well remain difficult. It thus seems possible that diseases depending on deficiency of an extracellular product, such as insulin, may be curable long before the bulk of hereditary diseases, where an externally supplied gene can benefit only those defective cells that have incorporated it and can then make the missing cell component.

Such a one-shot cure of a hereditary disease, if possible, would clearly be a major improvement over the current practice of continually supplying a missing gene product, such as insulin. (It could be argued that improving the soma in this way, without altering the germ cells, would help perpetuate hereditary defectives; but so does conventional medical therapy.) The danger of undesired side effects,

of course, would have to be evaluated, and the day-to-day medical use of such material would have to be regulated; but these problems do not seem to differ significantly from those encountered with any novel therapeutic agent.

*Germ cell alteration.*—Germ cells may prove more amenable than somatic cells to the introduction of DNA, since they could be exposed in the test tube and therefore in a more uniform and controllable manner. Another conceivable approach might be that of directed mutagenesis: the use of agents that would bring about a specific desired alteration in the DNA, such as reversal of a mutation that had made a gene defective. So far, however, efforts to find such directive agents have not been successful; all known mutagenic agents cause virtually random mutations, of which the vast majority are harmful rather than helpful. Indeed, before a mutagen could be directed to a particular site it would probably have to be attached first to a molecule that could selectively recognize a particular stretch of DNA (8); hence a highly selective mutagen would have to be at least as complex as the material required for selective genetic recombination.

If predictable genetic alteration of germ cells should become possible it would be even more useful than somatic cure of monogenic diseases, for it could allow an individual with a defective gene to generate his own progeny without condemning them to inherit that gene. Moreover, there would be a long-term evolutionary advantage, since not only the immediate product of the correction but also subsequent generations would be free of the disease.

*Genetic modification of behavior.*—In contrast to the cure of specific monogenic diseases, improvement of the highly polygenic behavioral traits would almost certainly require the replacement, in germ cells, of a large but specific complement of DNA. Since I find such replacement, in a controlled manner, very hard to imagine, I suspect that such modifications will remain indefinitely in the realm of science fiction, like the currently popular extrapolation from the transplantation of a kidney or a heart, with a few tubular connections, to that of a brain, with hundreds of thousands of specific neural connections. However, this consideration would not apply to the possibility of impairing cerebral function by genetic transfer, since certain monogenic diseases are known to cause such impairment.

*Copying by asexual reproduction (cloning).*—We now know that all the differentiated somatic cells of an animal (those from muscle, skin, and the like) contain, in their nuclei, the same complete set of genes. Every somatic cell thus contains all the genetic information required for copying the whole organism. In different cells different subsets of genes are active, while the remainder are inactive. Accordingly, if it should become possible to reverse the regulatory mechanism responsible for this differentiation any cell could be used to start an embryo. The individual could then be developed in the uterus of a foster mother, or eventually in a glorified test tube, and would be an exact genetic copy of its single parent. Such asexual reproduction could thus be used to produce individuals of strictly predictable

genetic endowment; and there would be no theoretical limit to the size of the resulting clone (that is, the set of identical individuals derivable from a single parent and from successive generations of copies).

Though differentiation is completely reversible in the cells of plants (as in the transfer of cuttings), it is ordinarily quite irreversible in the cells of higher animals. This stability, however, depends on the interaction of the nucleus with the surrounding cytoplasm; and it is now possible to transfer a nucleus, by microsurgery or cell fusion, into the cytoplasm of a different kind of cell. Indeed, in frogs differentiation has been completely reversed in this way: when the nucleus of an egg cell is replaced by a nucleus from an intestinal cell embryonic development of the hybrid cell can produce a genetic replica of the donor of the nucleus (9). This result will probably also be accomplished, and perhaps quite soon, with cells from mammals. Indeed, there is considerable economic incentive to achieve this goal, since the copying of champion livestock could substantially increase food production.

Another type of cloning can already be accomplished in mammals: when the relatively undifferentiated cells of an early mouse embryo are gently separated each can be used to start a new embryo (10). A large set of identical twins can thus be produced. However, they would be copies of an embryo of undetermined genetic structure, rather than of an already known adult. This procedure therefore does not seem tempting in man, unless the production of identical twins (or of greater multiplets) should develop social values, such as those suggested by Aldous Huxley in *Brave New World*.

*Predetermination of sex.*—Though no one has yet succeeded in directly controlling sex by separating XX and XY sperm cells, this technical problem should be soluble. Moreover, in principle it is already possible to achieve the same objective indirectly by aborting embryos of the undesired sex: for the sex of the embryo can be diagnosed by tapping the amniotic fluid (amniocentesis) and examining the cells released into the fluid by the embryo.

Wide use of either method might cause a market imbalance in the sex ratio in the population, which could lead to changes in our present family structure (and might even be welcomed in a world suffering from overpopulation). Alternatively, new social or legal pressures might be developed to avert a threatened imbalance (11). But though there would obviously be novel social problems, I do not think they would strain our powers of social adaptation nearly as much as some urgent present problems.

*Selective reproduction.*—A discussion of the prospects for molecular and cellular intervention in human heredity would be incomplete without noting that any society wishing to direct the evolution of its gene pool already has available an alternative approach: selective breeding. This application of classical, transmission genetics has been used empirically since Neolithic times, not only in animal husbandry, but also, in various ways (for example, polygamy, *droit de seigneur*, caste system), in certain human cultures. Declaring a moratorium on genetic research, in order to forestall possible future control of our gene pool, would therefore be locking the barn after the horse was stolen.

Having reviewed various technical possibilities, I would now like to comment on the dangers that might be presented by their fulfillment and to compare these with the consequences of efforts to prevent this development.

#### EVALUATION OF THE DANGERS

*Gene transfer.*—I have presented the view that if we eventually develop the ability to incorporate genes into human germ cells, and thus to repair monogenic defects, we would still be far from specifying highly polygenic behavioral traits. And with somatic cells such an influence seems altogether excluded. For though genes undoubtedly direct in considerable detail the pattern of development of the brain, with its network of connections of 10 billion or more nerve cells, the introduction of new DNA following this development clearly could not redirect the already formed network; neither could we expect it to modify the effect of learning on brain function.

To be sure, since we as yet have little firm knowledge of behavioral genetics we cannot exclude the possibility that a few key genes might play an especially large role in determining various intellectual or artistic potentials or emotional patterns. But even if it should turn out to be technically possible to tailor the psyche significantly by the exchange of a small number of genes in germ cells, it seems extremely improbable that this procedure would be put to practical use. For it will always be much easier, as Lederberg (12) has emphasized, to obtain almost any desired genetic pattern by copying from the enormous store already displayed in nature's catalog.

While the improvement of cerebral function by polygenic transfer thus seems extremely unlikely, one cannot so readily exclude the technical possibility of impairing this function by transfer of a monogenic defect. And having seen genocide in Germany and massive defoliation in Vietnam, we can hardly assume that a high level of civilization provides a guarantee against such an evil use of science. However, several considerations argue against the likelihood that such a future technical possibility would be converted into reality. The most important is that monogenic diseases, involving hormonal imbalance or enzymatic deficiencies, produce gross behavioral defects, whose usefulness to a tyrant is hard to imagine. Moreover, even if gene transfer is achieved in cooperating individuals, an enormous social effort would still be required to extend it, for political or military purposes, to mass populations. Finally, in contrast to the development of nuclear energy, which arose as an extension of already accepted military practices, the potential medical value of gene transfer is much more evident than its military value; hence a "genetic bomb" could hardly be sprung on the public as a secret weapon. Accordingly, we are under no moral obligation to sacrifice genetic advances now in order to forestall such remote dangers: if and when gene transfer in man becomes a reality there would still be time to assert the cultural and medical traditions that would promote its beneficial use and oppose its abuse.

This last obstacle would be eliminated if it should prove possible to develop a virus that could be used to infect a population secretly with

specific genes, and it is the prospect of this ultimate horror that seems to cause most concern. However, for reasons that I have presented above the technical possibility of producing useful modifications of personality by infections of germ cells seems extremely remote, and the possibility of doing so by infecting somatic cells in an already developed individual seems altogether excluded. These fears thus do not seem realistic enough to help guide present policy. Nevertheless, the problem cannot be entirely ignored: in a country that has recently been embarrassed by its accumulation of rockets containing nerve gas even the remote possibility of handing viral toys to Dr. Strangelove will require vigilance.

*Genetic copies.*—If the cloning of mammals becomes technically feasible its extension to man will undoubtedly be very tempting, on the grounds that enrichment for proved talent by this means might enormously enhance our culture, while the risk of harm seemed small. Since society may be faced with the need to make decisions in this area quite soon, I would like to offer a few comments in the hope of encouraging public discussion.

On the one hand, in fields such as mathematics or music, where major achievements are restricted to a few especially gifted people, an increase in their number might be enormously beneficial—either as a continuous supply from one generation to another or as an expanded supply within a generation. On the other hand, a succession of identical geniuses might exert an excessively conservative influence, depriving society of the richness that comes from our inexhaustible supply of new combinations of genes. Or genius might fail to flower, if its drive depended heavily on parental influence or on cultural climate. And in the literary, social, and political areas the cultural climate surely plays so large a role that there may be little basis for expecting outstanding achievement to be continued by a scion. The world might thus be quite disappointed by the contributions of another Tolstoy, Churchill, or Martin Luther King, or even another Newton or Mozart. Moreover, though experience with monozygotic twins is somewhat reassuring, persons produced by copying might suffer from a novel kind of “identity crisis.”

Though our system of values clearly places us under moral obligation to do everything possible to cure disease, there is no comparable basis for using cloning to advance culture. The responsibility for initiating such a radical departure in human reproduction would be grave, and surely many will feel that we should not do so. But I suspect that it would be impossible to enforce any such prohibition completely: the potential gain seems too large, and the procedure would require the cooperation of only a very small group of people. Hence whatever the initial social consensus, I suspect that a stable attitude would not emerge until after some early tests, whether legal or illegal, had demonstrated the magnitude of the problems and of the gains.

A much greater threat, I believe, would be the use of cloning for the large-scale amplification of a few selected individuals. Who would wish to send a child to a school with a large set of identical twins as his classmates? Moreover, the success of a species depends not only on its adaptation to its present environment but also on its possession of

sufficient genetic variety to include some individuals who could survive in any future environment. Hence if cloning were extended to the point of markedly homogenizing the population, it could create an evolutionary danger. However, we have already lived for a long time with a similar possibility: any male can provide a virtually limitless supply of germ cells, which can be used in artificial insemination; yet genetic homogenization by this means has not become the slightest threat. Since cloning is unlikely to become nearly so easy it is difficult to see a rational basis for the fear that its technical possibility would increase the threat.

*Implications for genetic research.*—Though the dangers from genetics seem to me very small compared with the immense potential benefits, they do exist: its applications could conceivably be used unwisely and even malevolently. But such potential abuses cannot be prevented by curtailing genetic research. For one thing, we already have on hand a powerful tool (selective breeding) that could be used to influence the human gene pool, and this technique could be used as wisely or unwisely as any future additional techniques. Moreover, since the greatest fear is that some tyrant might use genetic tools to regulate behavior, and especially to depress human potential, it is important to note that we already have on hand pharmacological, surgical, nutritional, and psychological methods that could generate parallel problems much sooner. Clearly, we shall have to struggle, in a crowded and unsettled world, to prevent such a horrifying misuse of science and to preserve and promote the ideal of universal human dignity. If we succeed in developing suitable controls we can expect to apply them to any later developments in genetics. If we fail—as we may—limitations on the progress of genetics will not help.

If, in panic, our society should curtail fundamental genetic research, we would pay a huge price. We would slow our current progress in recognizing defective genes and preventing their spread; and we would block the possibility of learning to repair genetic defects. The sacrifice would be even greater in the field of cancer: for we are on the threshold of a revolutionary improvement in the control of these malignant hereditary changes in somatic cells, and this achievement will depend on the same fundamental research that also contributes toward the possibilities of cloning and of gene transfer in man. Finally, it is hardly necessary to note the long and continuing record of nonmedical benefits from genetics, including increased production and improved quality of livestock and crops, steadier production based on resistance to infections, vastly increased yields in antibiotic and other industrial fermentations, and, far from least, the pride that mankind can feel in one of its most imaginative and creative cultural achievements: understanding of some of the most fundamental aspects of our own physical nature and that of the living world around us.

While specific curtailment of genetic research thus seems impossible to justify, we should also consider briefly the broader proposal (see, for example, 8) that we may have to limit the rate of progress of science in general, if we wish to prevent new powers from developing

faster than an inadequate institutional framework can be adjusted to handle them. While one can hardly deny that this argument may be valid in the abstract, its application to our present situation seems to me dangerous. No basis is yet in sight for calculating an optimal rate of scientific advance. Moreover, only recently have we become generally aware of the need to assess and control the true social and environmental costs of various uses of technology. Recognition of a problem is the first step toward its solution, and now that we have taken this step it would seem reasonable to assume, until proved otherwise, that further scientific advance can contribute to the solutions faster than it will expand the problems.

Another consideration is that we cannot destroy the knowledge we already have, despite its potential for abuse. Nor can we unlearn the scientific method, which is available for all who wish to wrest secrets from nature. So if we should choose to curtail research in various fundamental areas, out of fear of possible long-range application, we must recognize that other societies may make a different choice. Knowledge is power, and power can be used for good or for evil; and, since the genie that brings new knowledge is already out of the bottle, we must learn to direct the use of the resulting power rather than curse the genie or try to confine him.

We cannot see how far the use of science as a scapegoat for many of our social problems will extend. But the gravity of the threat may be underscored by recalling that another politically based attack on science, Lysenkoism, utterly destroyed genetics in the Soviet Union and seriously crippled agriculture, from 1935 to 1965 (13). [This development illustrates ironically the unstable relation between political and scientific ideas: for Karl Marx had unsuccessfully requested permission to dedicate the second volume of *Das Kapital* to Charles Darwin (14)!] Moreover, the current attacks on genetics from the New Left can build on, and have no doubt contributed to, widespread public anxiety concerning gene technology. Thus while a recent report prepared for the American Friends Service Committee (15) presents an open and thoughtful view on such questions as contraception, abortion, and prolongation of the period of dying, it is altogether opposed to any attempted genetic intervention, including the cure of hereditary disease.

Genetics will surely survive the current attacks, just as it survived attacks from the Communist Party in Moscow and from fundamentalists in Tennessee. But meanwhile if we wish to avert the danger of some degree of Lysenkoism in our country we may have to defend vigorously the value of objective and verifiable knowledge, especially when it comes into conflict with political, theological, or sociological dogmas.

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## D. GENE THERAPY FOR HUMAN GENETIC DISEASE?\*

PROPOSALS FOR GENETIC MANIPULATION IN HUMANS RAISE DIFFICULT  
SCIENTIFIC AND ETHICAL PROBLEMS

(By Theodore Friedmann and Richard Roblin\*\*)

At least 1,500 distinguishable human diseases are already known to be genetically determined (1), and new examples are being reported every year. Many human genetic diseases are rare. For example, the incidence of phenylketonuria is about one per 18,000 live births or about 200 to 300 cases per year in the United States (2). Others, such as cystic fibrosis of the pancreas, occur about once in every 2,500 live births (3). When considered together as a group, however, genetic diseases of humans are becoming an increasingly visible and significant medical problem, at least in the developed countries. While the molecular basis for most of these diseases is not yet understood, a recent review (4) listed 92 human disorders for which a genetically determined specific enzyme deficiency has been identified.

Concurrent with the recent progress toward biochemical characterization of human genetic diseases have been the dramatic advances in our understanding of the structure and function of the genetic material, DNA, and our ability to manipulate it in the test tube. Within the last 3 years, both the isolation of a piece of DNA containing a specific group of bacterial genes (5) and the complete chemical synthesis of the gene for yeast alanine transfer RNA (6) have been reported. These advances have led to proposals (7) that exogenous "good" DNA be used to replace the defective DNA in those who suffer from genetic defects. In fact, a first attempt to treat patients suffering from a human genetic disease with foreign DNA has already been made (8).

Nevertheless, we believe that examination of the current possibilities for DNA-mediated genetic change in humans in the light of some of the requirements for an ethically acceptable medical treatment raises difficult questions. In order to focus the discussion, in this article we concentrate on the prospects for using isolated DNA segments or mammalian viruses as vectors in gene therapy. For this reason we do not discuss other techniques, such as cell hybridization (9), which have been used to introduce new genetic material into mammalian cells. We limit our discussion to the possible therapeutic uses of genetic engineering in humans. The potential eugenic uses, for example, the improvement of human intelligence or other traits, are not discussed because they will be very much more difficult to accomplish (10) and raise rather different ethical questions. Whether

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genetic engineering techniques can be developed for therapeutic purposes in human patients without leading to eugenic uses is an important question, but lies mostly beyond the scope of this article.

#### *Schematic Model of Genetic Disease*

Some aspects of a hypothetical human genetic disease in which an enzyme is defective are shown in figure 1. The consequences of a gene mutation which renders enzyme  $E_3$  defective could be (i) failure to synthesize required compounds D and F; (ii) accumulation of abnormally high concentrations of compound C and its further metabolites by other biochemical pathways; (iii) failure to regulate properly the activity of enzyme  $E_1$ , because of loss of the normal feedback inhibitor, compound F; and (iv) failure of a regulatory step in a linked pathway because of absence of compound D or F, as in the increased synthesis of ketosteroids in the adrenogenital syndrome (11). In some cases of human genetic disease, accumulation of high concentrations of compound C and its metabolites appears to do the damage. Often a consequence is mental retardation.

The pathway in figure 1 is typical of some recessively inherited genetic defects which result in a deficiency of some gene product, usually an enzyme or hormone. In theory, such defects might be corrected by gene therapy, since such techniques might be able to restore the deficient gene product. Other kinds of genetic defects, including those such as the Marfan syndrome which show dominant inheritance and those such as Mongolism that are caused by chromosome abnormalities, could probably not be ameliorated by the kind of gene therapy we emphasize here.

#### *Current Therapy*

Human genetic diseases are usually treated by dietary therapy (12), drug therapy, or gene product replacement therapy (11). For example, diets low in lactose or phenylalanine are used as treatments for individuals with galactosemia and phenylketonuria, respectively. Such diets have proved exceedingly effective in galactosemia and have produced a marked reduction in the incidence of mental retardation associated with phenylketonuria. In terms of figure 1 this therapy corresponds to restricting the intake of compound A, thus minimizing the accumulation of compound C whose further normal metabolism is blocked.

Drug therapy has been used to block or reduce the accumulation of undesired and possibly harmful metabolites. One example is the inhibition of the enzyme xanthine oxidase with the drug allopurinol to reduce the accumulation of uric acid associated with gout and the Lesch-Nyhan syndrome (13). At present, this method of treatment has been applied to only a few human genetic diseases. Its more general application clearly depends upon the availability of drugs which act selectively on specific enzymes. In another form of drug therapy, drugs which combine specifically with the accumulated compound C are used. An example is the use of D-penicillamine to promote excretion of excess cystine in patients with cystinuria (11).

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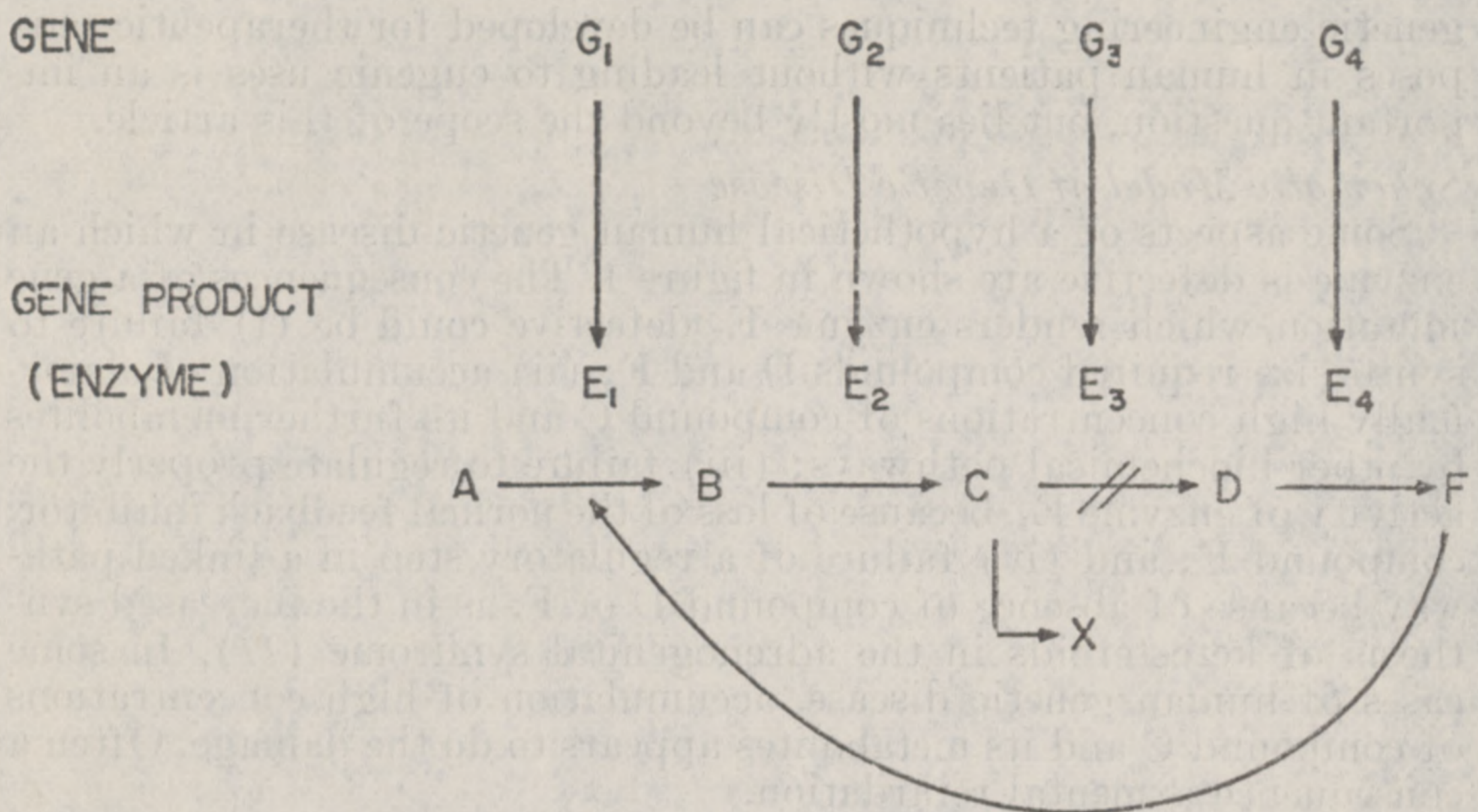


FIGURE 1.—A hypothetical pathway for the enzymatic conversion of compound A to a final metabolic product F. Compounds B, C, and D are intermediate products. Four different enzymes, E<sub>1</sub>, E<sub>2</sub>, E<sub>3</sub>, and E<sub>4</sub>, the products of the corresponding genes G<sub>1</sub>, G<sub>2</sub>, G<sub>3</sub>, and G<sub>4</sub> are required to effect the conversion. The block occurs in the conversion of compound C to D. The concentration of compound F regulates the activity of the first enzyme in the pathway, E<sub>1</sub>, in a feedback control loop.

In theory, some human genetic diseases might be alleviated by supplying directly the deficient enzyme (E<sub>3</sub> in fig. 1). Recently, attempts to treat Fabry's disease (14), metachromatic leukodystrophy (15), and type 2 glycogenosis (16), by administering the missing enzyme have been reported. Since exogenous enzyme molecules are eventually inactivated or excreted from the body, repeated enzyme injections would be required to manage the diseases in this way. In time, the patients would probably respond by forming antibodies against the administered enzyme. However, insoluble or encapsulated enzyme preparations may in the future provide a means of supplying therapeutic enzymes in a more stable and perhaps less immunogenic form.

There are growing possibilities for the early detection of some genetic diseases by diagnosis in utero. It is now possible to sample the cells of a growing fetus in utero and by examining these cells to diagnose a variety of genetic defects (17). If genetic defects are detected, some States will permit an abortion if the prospective parents so desire. We recognize that diagnosis in utero and abortion raise difficult social and ethical problems of their own and cite them only to indicate that there are additional alternatives to prospective gene therapy for coping with human genetic disease.

However, many genetic diseases do not yet respond to any of these treatments. For example, most genetic disorders of amino acid metabolism (other than phenylketonuria) cannot be well controlled by dietary therapy. Storage diseases associated with lysosomal enzyme deficiencies (18) do not appear to respond to enzyme therapy (14, 15) and will probably be impossible to control by dietary restriction. In

addition, even in cases where disease management is effective, it is seldom perfect. Individuals with diabetes mellitus, when treated with insulin, have an increased incidence of vascular and other disorders and a decreased life expectancy compared to the nondiabetic population (19). Children with Lesch-Nyhan syndrome may have their uric acid accumulation controlled by drug (allopurinol) therapy, but their brain dysfunction has, to date, not been reversible.

These limitations of current therapy are stimulating attempts to develop techniques for treating human genetic diseases at the genetic level, the site of the primary defect. Genetic modification of specific characteristics of human cells by means of exogenous DNA seems possible for several reasons. DNA-mediated genetic modification of several different kinds of bacteria has been known for many years (20), and recent experiments suggest that the genetic properties of mutant *Drosophila* strains can be modified by treating their eggs with DNA extracted from other *Drosophila* strains (21). It has also been found that treatment of human cells in-vitro with DNA extracted from the oncogenic virus SV40 results in permanent heritable alteration of several cellular properties (22).

#### *Genetic Modification Mediated by DNA*

Permanent, heritable, genetic modification of a human cell by means of DNA requires (i) uptake of the exogenous DNA from the extracellular environment; (ii) survival of at least a portion of the DNA during its intracellular passage to the nucleus; (iii) stabilization of the exogenous DNA in the recipient cell; and (iv) expression of the new genes via transcription into an RNA message (mRNA) and translation of this message into the appropriate protein. Some of these processes are illustrated schematically in figure 2.

Mammalian cells take up proteins, nucleic acids, and viruses from their environment by a process known as endocytosis (23). After binding to the cell membrane, the macromolecules are drawn into the cell by an infolding of the external cell membrane leading to vesicle formation (see figure 2). Macromolecules contained in vesicles derived from invaginations of the external cell membrane can be degraded if these vesicles fuse with lysosomes. Lysosomes are cell organelles which contains a variety of hydrolytic enzymes. These enzymes can rapidly degrade ingested macromolecules, including DNA (24). Thus, mammalian cells possess mechanisms for protecting themselves from the potentially perturbing influences of foreign DNA.

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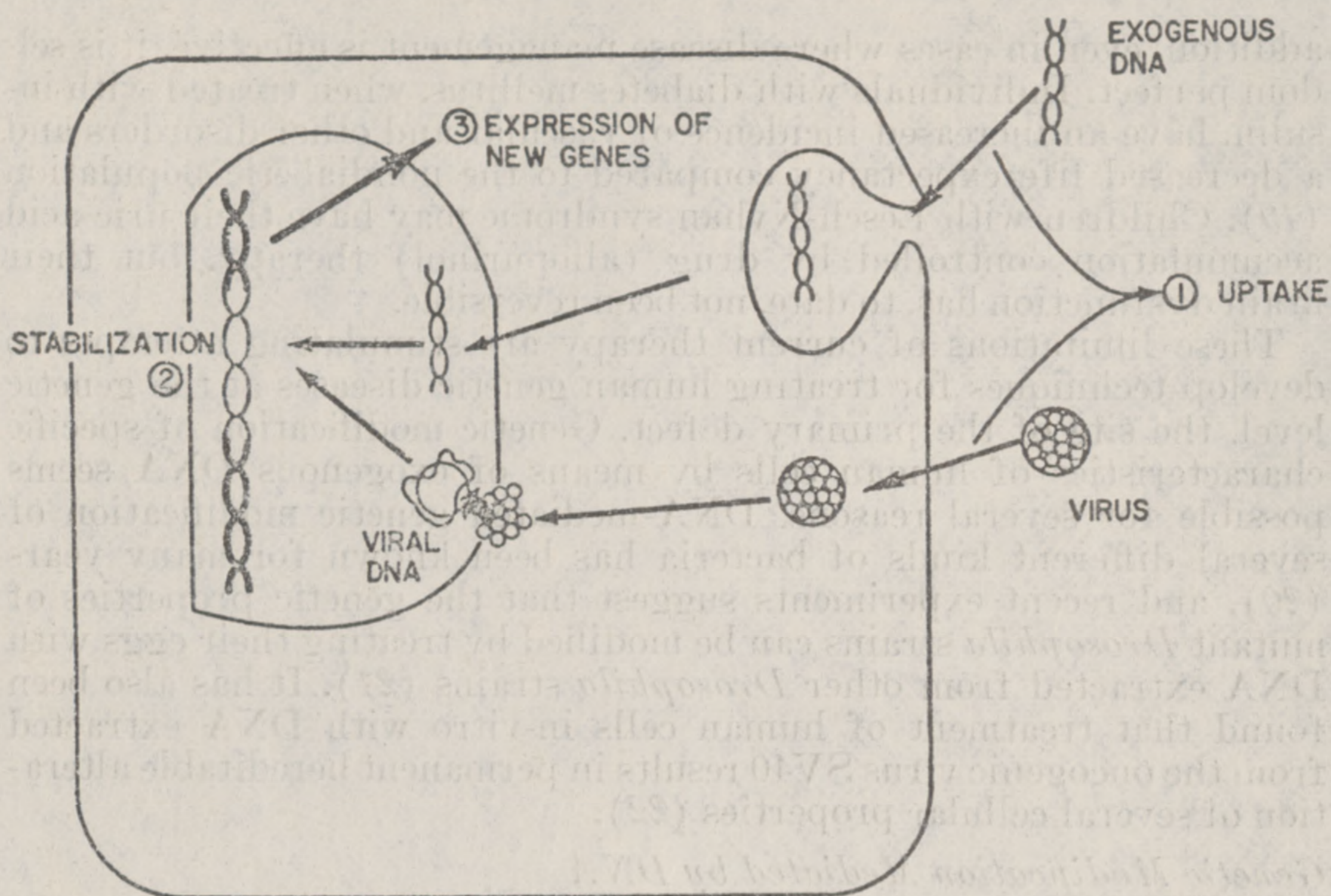


Figure 2. Steps in the genetic modification of a mammalian cell. The added exogenous genetic information may be integrated into the chromosome of the recipient cell and become expressed as a new gene product.

Despite this cellular defense mechanism, exogenous foreign DNA can under certain circumstances, become integrated in the DNA of the recipient cell. The evidence of this has come from studies of oncogenic virus transformation of mammalian, including human, cells (25). In the case of oncogenic transformation with SV40 virus, the viral DNA is apparently physically integrated into the chromosomal DNA of the recipient cell (26). It seems probable that heritable alterations of cell morphology and biochemistry are the result of the expression of one or more viral genes. Presumably, viral DNA integration takes place by base pairing of homologous regions of host cell and viral DNA followed by genetic recombination. However, the integration of oncogenic viral DNA may represent a special case since at least one viral gene product may be required for integration (27). Other, nonviral DNA molecules, unable to supply this integration function, might integrate at a much lower frequency, if at all.

In addition to integration by genetic recombination, exogenous DNA might be stabilized in the recipient mammalian cell as an independently replicating genetic unit in the cell nucleus. Although such units are known to exist in bacteria, they have not been observed in mammalian cells. However, the cytoplasmic mitochondria of mammalian cells do contain nonchromosomal, independently replicating units of DNA. The mitochondrial DNA replication system thus offers another possible site for stabilization of exogenous DNA.

For a human genetic defect to be repaired by administering exogenous DNA, the stabilized newly introduced DNA must be correctly expressed. That is, the new gene must be correctly transcribed into

mRNA and this mRNA must be correctly translated into protein. Since little is known about the regulation of mRNA synthesis and translation during natural gene expression in mammalian cells, a corresponding high degree of uncertainty exists concerning the ability of newly introduced DNA to be expressed correctly.

A variety of attempts have been made to demonstrate DNA-mediated modification of genetically mutant mammalian cells, both in vivo and in vitro. Apparently successful results in vitro have been reported for diploid human cells lacking the purine "salvage" enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT); in human reticulocytes synthesizing an abnormal hemoglobin; in several malignant cells of mouse origin carrying markers for drug resistance; and in mouse cells with defective melanin synthesis, among others (28). In addition, transient expression of HGPRT enzyme function has been detected in human cells deficient in HGPRT after exposing them to DNA from cells with normal amounts of HGPRT (29). This suggests that exogenous DNA may be taken up and expressed, without necessarily being stabilized. However, none of the successful experiments described to date have been reproducible.

There may be several reasons for failure to demonstrate consistently the genetic modification of mammalian cells by DNA. Many previous experiments suffered from the unavailability of good genetic markers and sensitive selective systems for detecting modified cells. An important difficulty in using bulk DNA isolated from human (or other mammalian) cells is that the fraction of this DNA which is specific for any given gene is estimated to be extremely small, of the order of  $10^{-7}$  (30). As we mentioned earlier, nonviral exogenous DNA may not be able to integrate into the chromosomal DNA of the recipient cell, thus preventing permanent genetic modification.

In spite of the lack of reproducible success in past experiments, several recent technical developments have suggested new ways in which the problems of low DNA specificity, failure of integration, and intracellular DNA degradation might be overcome.

The prospects for directing genetic modification of mammalian cells would almost certainly be enhanced by using DNA preparations containing only the gene for which the genetically defective cells are mutant. As already pointed out, both the isolation of a specific group of bacterial genes and the complete chemical synthesis of a single gene were reported recently (5, 6).

The RNA-dependent DNA polymerase recently found in RNA tumor viruses (31) could also be used for gene synthesis in vitro. Since this enzyme is able to make DNA copies from an RNA template, it offers a method for synthesizing the DNA for any specific RNA which might be isolated in pure form. Thus, it seems probable that our developing ability to isolate specific genes, or synthesize them, will eventually eliminate the problem of low specificity of the exogenous DNA.

Some workers are developing techniques which could be used to overcome the problem of stabilizing the incoming exogenous DNA in the recipient cell (32). They plan to make use of the ability of the DNA from SV40 virus to integrate into the chromosomal DNA of the

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cell. Specific genes will be attached to the viral DNA by means of several biochemical steps which are already known and fairly well characterized. These operations would create a hybrid DNA molecule which would carry the information for integration from the original viral DNA and perform the specific gene functions of the attached DNA. In this approach, DNA integration would be combined with biochemical manipulation of the DNA gene substance *in vitro*, and any gene-specific DNA segments obtained by synthesis or isolation could be utilized. It is clear that before such hybrid DNA molecules could be used in a human therapeutic situation, the oncogenic potential of the viral DNA would have to be eliminated.

In another experimental approach, virus-like particles which contain pieces of cellular DNA (pseudovirions) instead of viral DNA are being used as the vector for DNA-mediated genetic modification (33). This might help to protect the incoming DNA from intracellular degradation. However, pseudovirion DNA is probably a random collection of cellular DNA fragments (34) and hence nonspecific for any given gene; it might also be unable to stabilize itself by integration into the host cell DNA. This may explain why attempts to modify thymidine kinase-deficient mouse cells *in vitro* by means of polyoma virus pseudovirions have been unsuccessful (35).

It has recently proved possible to reconstruct infectious particles of several plant and bacterial viruses from the nucleic acid and capsid protein components (36). This suggests the possibility of creating artificial pseudoviruses as vectors for DNA-mediated genetic modification. These pseudovirions would contain specific DNA segments (either isolated or synthesized) surrounded by virus capsid protein. The probability of introducing a specific piece of genetic material might be greatly increased when compared with natural pseudovirions carrying randomly excised pieces of DNA. This in no way solves the difficulties of integration and expression of the genetic material. Since the specificity of virus-cell interactions is determined at least in part by the virus capsid protein, encapsidation of specific DNA molecules might confer some cell or tissue selectivity upon the DNA molecules used for gene modification.

#### *DNA-Mediated Gene Therapy*

In attempting to envision how DNA might be used as a mediator for the modification of genes in a human being suffering from a genetic defect, we foresee several kinds of new problems. First, the existence of differentiation and cell specialization in the human body will pose several questions. Many human genes are active or expressed only in a small fraction of the cells of the body. For example, the activity of the enzyme phenylalanine hydroxylase (deficient in individuals with phenylketonuria) is demonstratable only in the liver. For prospective gene therapy there might be several consequences. (i) The introduction of, for example, the gene for phenylalanine hydroxylase into cells which do not normally express this enzyme would yield no therapeutic benefits if the expression of the newly introduced genes were also blocked. Methods would have to be developed to deliver the exogenous DNA to the appropriate "target tissue," and to confine its

action solely to that tissue. (ii) Some gene products (hormones, for example) are made and secreted by one specialized group of cells and act on target cells elsewhere in the body. Synthesis and secretion of hormones such as insulin are regulated by mechanisms which are still imperfectly understood. Thus, the introduction of new genes for insulin into cells not appropriately differentiated to provide the correct synthetic and secretory responses would be of little use as a treatment for diabetes. (iii) In several genetic disorders, genetic modification of the brain cells themselves may be required to reduce the accumulation of metabolite in the brain, because the blood-brain barrier might prevent enzymes made in other parts of the body from entering the brain (15). We wonder whether direct genetic modification of brain cells could be made safe enough for use in human patients.

Second, regulation of the quantitative aspects of enzyme production may present a problem. By mechanisms as yet unknown, concentrations of cellular enzymes are regulated so that neither too much nor too little enzyme is produced by normal cells. How will we ensure that the correct amount of enzyme will be made from the newly introduced genes? Will the integration event, linking exogenous DNA to the DNA of the recipient cell, itself disturb other cellular regulatory circuits?

Third, the patient's immunological system must not recognize as foreign the enzyme produced under the direction of the newly introduced genes. If this occurred, the patient would form antibodies against the enzyme protein, perhaps nullifying the intended effects of the genetic intervention. This suggests that the new gene introduced during gene therapy would have to code for an enzyme with the same amino acid sequence as the human enzyme.

In addition, administration of foreign genetic material to patients carries a risk of altering the germ cells as well as the desired target cells. One might think that this problem could be circumvented by first removing some of the patients' cells, carrying out DNA-mediated genetic modification *in vitro*, and then reimplanting the altered cells back into the patient. However, this approach is likely to be limited by the tendency of cells to dedifferentiate and become malignant when grown *in vitro*.

For an acceptable genetic treatment of a human genetic defect, we would require that the gene therapy replace the functions of the defective gene segment without causing deleterious side effects either in the treated individual or in his future offspring. Years of work with tissue cultures and in experimental animals with genetic defects will be required to evaluate the potential side effects of gene therapy techniques. In our view, solutions to all these problems are needed before any attempt to use gene therapy in human patients could be considered ethically acceptable.

We are aware, however, that physicians have not always waited for a complete evaluation of new and potentially dangerous therapeutic procedures before using them on human beings. Consider how little was known of the basic aspects of virology during Jenner's development of vaccination against smallpox. In this regard, potential gene

therapy techniques resemble other medical innovations. There is currently, and there may continue to be, a tendency to use incompletely understood genetic manipulative techniques, borrowed from molecular biology, in clinical settings. We believe that the first attempt at gene therapy in human patients (8) illustrates this contention.

The case in question (8) concerns two children suffering from hyperargininemia, a hereditary deficiency of the enzyme arginase. The arginase deficiency leads to high concentrations of arginine in the children's blood and cerebrospinal fluid, and has associated with it severe mental retardation (37). An attempt has been made to correct this defect at the genetic level by injecting Shope papilloma virus into the children (8). The scientific rationale for this treatment is based upon the report that the synthesis of arginase is stimulated in rabbit skin infected with Shope papilloma, and that this new arginase activity had some properties which are different from those of the normal enzyme of rabbit liver (38). In 1958, when these experiments were first reported, it was postulated that the viral DNA carried the gene for a viral arginase different from the cellular enzyme. In addition, the serums of laboratory workers who had worked with and thus been exposed to Shope papilloma virus were tested, and 35 percent of them exhibited lower concentrations of arginine than control hospital patients who had not knowingly been exposed to the virus (39). Thus, there were some grounds for believing that inadvertent infection with Shope papilloma in humans could lower the concentration of serum arginine without apparent harmful effects.

More recently, the interpretation that Shope papilloma virus codes for an arginase has been seriously questioned (40). It now appears more probable that the virus infection stimulates the production of a cellular arginase. Whether the induced arginase is coded for by viral or by cellular genes is important to the rationale of this attempt at gene therapy. If virus infection induces the synthesis of cellular arginase, and if the children have hereditarily lost the ability to produce arginase, then infecting the children with Shope papilloma virus may not have any possibility of correcting their condition (41).

The use of intact viruses as vectors in gene therapy raises further questions. When applied to the skin of rabbits Shope papilloma virus induces skin papillomas, a variable proportion of which develop into cancerous skin lesions. Although Shope papilloma has not had any known harmful effects on humans, tests to establish the safety of large doses have not been performed. It should also be shown that a vector for clinical gene therapy is free from other contaminating viruses latent in the cells used to produce the injected virus.

The clinical results of this therapeutic attempt are not yet known. But we are concerned that this first attempt at gene therapy, which we believe to have been premature, will serve as an impetus for other attempts in the near future. For this reason, we offer the following considerations as a starting point for what we hope will become a widespread discussion of appropriate criteria for the use of genetic manipulative techniques in humans.

### *Some Preliminary Criteria*

We proposed the following ethico-scientific criteria which any prospective techniques for gene therapy in human patients should satisfy:

1) There should be adequate biochemical characterization of the prospective patient's genetic disorder. It should be determined whether the patient (i) is producing a mutated, inactive form of the normal protein; (ii) is producing none of the normal protein; or (iii) is producing the normal protein in normal amounts, but the protein is rendered inactive in some way. For example, alterations in membrane structure leading to loss of the cellular receptors for insulin could produce a diabetes-like condition, even though the patient were producing normal amounts of insulin. We anticipate the defects of this type may be found affecting the activity of enzymes which are normally constituents of cell membranes. Our point is that only in the first type of genetic defect (i) would currently envisioned gene therapy techniques be likely to improve the patient's condition.

2) There should be prior experience with untreated cases of what appears to be the same genetic defect so that the natural history of the disease and the efficacy of alternative therapies can be assessed. Thus, the first reported cases of a new human genetic disease would seldom be candidates for attempts at gene therapy. The reason for this criterion comes from our accumulating experience with some of the better studied genetic defects such as phenylketonuria and galactosemia. We now observe heterogeneity in these conditions; that is, what appears to be the same genetic disease turns out to have different genetic bases in different individuals. Widespread screening for phenylketonuria in newborns has detected individuals who, like phenylketonurics, have high concentrations of phenylalanine in the serum just after birth, but have concentrations in the normal range several months later (2). It is now also clear that some individuals with high concentrations of phenylalanine in the serum have normal intelligence quotients (2). We anticipate that other genetic diseases will exhibit the same kind of heterogeneity. Concern for the welfare of each individual patient dictates that we not rush in with gene therapy until we are very sure about the precise nature and consequences of his genetic defect.

3) There must be an adequate characterization of the quality of the exogenous DNA vector. This will require the development of new, more accurate methods of analyzing the base sequence of the DNA, if synthetic DNA molecules are to be used, or the development of new methods of isolation and purification, if naturally occurring DNA molecules are to be used. We visualize the Food and Drug Administration, or some similar organization, establishing and enforcing quality standards for DNA preparations used in gene therapy.

4) There should be extensive studies in experimental animals to evaluate the therapeutic benefits and adverse side effects of the prospective techniques. These tests should include long-term studies on the possible induction of cancer and genetic disturbances in the offspring of the treated animals. This will require the development of animal models for human genetic diseases. Previous work, which led to the isolation of the mouse strain deficient in the enzyme catalase (42),

suggests that such animal models could be developed and might yield answers to some of the questions we have raised.

5) For some genetic diseases, the patient's skin fibroblasts grown *in vitro* reflect the disorder. Thus, in some cases it would be possible to determine whether the prospective gene therapy technique could restore enzyme function in the cells of the prospective patient. This could be done first *in vitro*, without any of the risks of treating the whole patient. Some side effects, such as chromosome damage and morphological changes suggesting malignancy, could also be assessed at this time. Only when a potential gene therapy technique had satisfied all these safety and efficacy criteria would it be considered for use in human patients.

These criteria omit some other considerations which we believe are important. Although the ethical problems posed by gene therapy are similar in principle to those posed by other experimental medical treatments, we feel that the irreversible and heritable nature of gene therapy means that the tolerable margin of risk and uncertainty in such therapy is reduced. Physicians usually arrive at a judgment regarding the ethical acceptability of an experimental therapy by balancing the risks and consequences of different available treatments against their potential benefits to the patient. In general, the degree of risk tolerated in medical treatment is directly related to the seriousness of the condition.

High-risk treatments are sometimes considered more justified in life-threatening situations. For different human genetic diseases, the severity of the problem in the untreated condition and the response to currently available therapy varies greatly. Thus, phenylketonuria leads to mental retardation, but not death, in most untreated affected individuals, but the mental retardation can be avoided for the most part by prompt neonatal dietary therapy. In contrast, in the infantile form of Gaucher's disease, a deficiency in the enzyme glucocerebrosidase (important in the metabolism of brain glycolipids) leads to severe and progressive neurologic damage and death within 1 or 2 years (38). There is as yet no effective therapy. Thus, the specific characteristics of each genetic disease will be an important factor in evaluating whether or not to attempt gene therapy. We believe that the prospective use of gene therapy will need to be evaluated on a case by case basis.

Another ethical ideal which guides experimental medical treatments is informed consent. By informed consent we mean that the patient, after having the nature of the proposed treatment and its known and suspected risks explained to him by the physician, freely gives the physician his consent to proceed with the treatment. Since many of the cases where gene therapy might be indicated will involve children or newborns as patients, there will be especially troubling problems surrounding informed consent. Parents of newborn children with genetic defects may be asked to give "consent by proxy" for gene therapy. Clearly, until we know much more about the side effects of gene therapy, it will not be possible to provide them with adequate information about risks to the treated individual and his offspring.

### *Control of Gene Therapy*

How can gene therapy in humans be controlled to avoid its misuse? By misuse we mean the premature application of techniques which are inadequately understood and the application of gene therapy for anything other than for the primary benefit of the patient with the genetic disease. In our view, it will be possible to control the procedures used for gene therapy at several levels. For example, between the patient and physician, we can usually rely upon the selection of a therapeutic technique having optimal chances of success. In general, we believe that the doctor will not recommend and the patient will not accept an uncertain, risk-laden gene therapy if a reasonably effective alternative therapy is available. However, the physician, in this as in other cases of experimental therapeutic techniques, has a near monopoly on the relevant facts about risks and benefits of various treatments. Since the physician concerned may also be active in trying to develop the gene therapy technique, how can the patient be protected from a physician who might be overeager to try out his new procedure?

It seems to us that significant opportunities for control also exist at the level of the hospital committees responsible for examining experimental techniques. Already at accredited hospitals, all proposals for research in which human subjects will be used must pass through a review committee. Further control exists through scrutiny of the proposed techniques by the physician's immediate peers.

Procedures to be used for gene therapy might also be controlled by the committees and organizations approving and funding research grants. Moderately large amounts of money will be required for the development of gene therapy techniques, hence there should be competition for public funds with other urgent medical needs. Thus, the first use of gene therapy in human patients would, of necessity, have secured the implied or direct approval of several larger public bodies beyond the principal physician-investigator. In our judgment, these levels of control will probably prove adequate to prevent misuse of projected gene therapy if, as we suspect, gene therapy is attempted in only a small number of instances. Any potential large-scale use of gene therapy (for example, the prospect of treating the approximately 4 million diabetics in the United States with DNA containing the gene for insulin) might appreciably affect the overall quality of the gene pool and would require other forms of control.

### *Conclusions*

In our view, gene therapy may ameliorate some human genetic diseases in the future. For this reason, we believe that research directed at the development of techniques for gene therapy should continue. For the foreseeable future, however, we oppose any further attempts at gene therapy in human patients because (i) our understanding of such basic processes as gene regulation and genetic recombination in human cells is inadequate; (ii) our understanding of the details of the relation between the molecular defect that the disease state is rudimentary for essentially all genetic diseases; and (iii) we have no

information on the short-range and long-term side effects of gene therapy. We therefore propose that a sustained effort be made to formulate a complete set of ethicoscientific criteria to guide the development and clinical application of gene therapy techniques. Such an endeavor could go a long way toward ensuring that gene therapy is used in humans only in those instances where it will prove beneficial, and toward preventing its misuse through premature application.

Two recent papers have provided new demonstrations of directed genetic modification of mammalian cells. Munyon et al. (44) restored the ability to synthesize the enzyme thymidine kinase to thymidine kinase-deficient mouse cells by infection with ultraviolet-irradiated herpes simplex virus. In their experiments the DNA from herpes simplex virus, which contains a gene coding for thymidine kinase, may have formed a heritable association with the mouse cells. Merrill et al. (45) reported that treatment of fibroblasts from patients with galactosemia with exogenous DNA caused increased activity of a missing enzyme,  $\alpha$ -D-galactose-1-phosphate uridylyltransferase. They also provided some evidence that the change persisted after subculturing the treated cells. If this latter report can be confirmed, the feasibility of directed genetic modification of human cells would be clearly demonstrated, considerably enhancing the technical prospects for gene therapy.

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## E. BABIES BY MEANS OF IN VITRO FERTILIZATION: UNETHICAL EXPERIMENTS ON THE UNBORN?

(By Leon R. Kass, M.D., Ph. D.\*\*)

### ABSTRACT

The coming technologies of human reproduction pose many difficult and important ethical and social problems. A major question concerns the propriety of perfecting these technologies by experiments on the unborn and the unconceived. Because the new procedures for in vitro fertilization and laboratory culture of human embryos probably carry a serious risk of damage to any child so generated, there appears to be no ethical way to proceed. One cannot ethically choose for a child the unknown hazards that he must face, and simultaneously choose to give him life in which to face them. Also, one must be careful to avoid exploiting the desires and hopes of childless couples. The medical and scientific communities ought to assume the major responsibility for scrutinizing and regulating the human use of new technologies emerging from research into human reproduction.

Since the disclosure of the unspeakable experiments performed by Nazi physicians and scientists upon helpless human beings, there has been a growing interest in the difficult and important questions concerning the use of human subjects in experimentation (1)–(8). The principle of informed consent has been enshrined as the ideal toward which many practical steps are being and still need to be taken. By making an effort to obtain consent, the physician investigator is restrained from using human beings simply as means to his own ends; by giving his consent, the subject becomes a coadventurer with the physician investigator in the search for new knowledge or new remedies for disease. But although there is agreement on what ought to be, many difficulties remain in achieving informed consent in practice.

Experimentation on children poses special problems. Because a child cannot give a truly informed and voluntary consent, some have argued that all nontherapeutic experimentation (i.e., research from which the subjects cannot hope to derive therapeutic benefit) is unethical. Others, although conceding the force of this objection, argue that the physician has a moral duty to seek new means for healing sick children—means that can only be obtained by experimenting on them. Thus, in the matter of experimentation on children, disagreement on what ought to be done complicates the difficult task of assuring ethical practices.

Given these theoretical and practical problems in achieving ethical experimentation on existing human beings, it is not surprising that little attention has been paid to questions concerning experiments upon the unborn. Yet coming developments, including genetic manip-

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ulation of embryos or even gametes, surely will raise large ethical questions. More immediately, we face similar questions in connection with recently acquired abilities to initiate human life *in vitro*. This paper is an attempt to generate discussion of the ethics of experimenting on the unborn and the conceived.

#### IN VITRO FERTILIZATION IN HUMANS—STATE OF THE ART

Several laboratories have recently reported the *in vitro* fertilization of human egg by human sperm, and the subsequent laboratory culture of the zygote up to the blastocyst stage (9)–(13). To surmount the difficulty of recovering eggs after their release from the ovary, Drs. P. C. Steptoe and R. G. Edwards have devised a surgical method, involving laparoscopy, to remove matured eggs directly from their follicles before ovulation (14). From one woman, as many as three or four preovulatory oocytes can be recovered. Upon addition of sperm, fertilization occurs with a small but appreciable fraction of these eggs. Kept in culture medium, a majority of the fertilized eggs begin to divide, and a small fraction reaches the blastocyst stage, the stage at which the early embryo normally implants itself in the endometrium. Successful implantation of laboratory-grown blastocysts has been reported in rabbits and in mice, but not in humans (15)–(17). The results in mice can be considered to be somewhat encouraging. A recent article reports that nearly half the transferred blastocysts developed into full-term, apparently normal progeny; however, the yield over all stages was low, with only 4 percent of the starting number of eggs giving rise at the end to viable mice (17). No gross abnormalities have been noted in any of the animals born alive after blastocyst transfer. And although some researchers would prefer to learn more about the control of implantation in animals before proceeding further in the human work, others are inclined to go ahead in humans on a trial-and-error basis.

#### ETHICS OF EXPERIMENTING ON THE UNBORN AND THE UNCONCEIVED

My discussion of ethical issues will consider only attempts to produce a child for a childless couple. Thus, I am concerned here with the proposed implantation experiments, and not with laboratory fertilization itself. I shall examine some limited questions concerning the ethics of experimenting on human subjects, questions that will also apply to all proposed uses of this and future technologies to start new human lives. Other, broader questions in need of discussion lie beyond the scope of this paper; I have explored some of them elsewhere (18).

The use of *in vitro* fertilization to initiate a new human life involves the necessary and deliberate manipulation of a human embryo, conceived and nurtured, at least for a time, in an artificial environment. Serious questions can be raised about the safety of the manipulations and of the environment and, hence, about the “normality” of any child whose conception and early development were subject to such manipulation. These medical questions about safety and “normality” lead to a perplexing moral question, since the hazards are being imposed on

another human being, the prospective child, who obviously cannot consent to have such risks imposed upon him. The moral question is this: Does the parents' desire for a child (or the obstetrician's desire to help them) entitle them to have it by methods that deliberately impose upon that child an unknown and untested risk of deformity or malformation?

How unknown are the risks? Some of the leading researchers appear to disagree. Drs. Edwards and Steptoe are reported ready to proceed with implantation if tests on the embryos can rule out the presence of genetic or other defects (according to an article by Walter Sullivan in the *New York Times*, for October 29, 1970). Apparently, they are both concerned about the risks and ignorant of their likelihood. In their judgment, "[t]he normality of embryonic development and efficiency of embryo transfer cannot yet be assessed" (10). In contrast, Dr. Landrum Shettles does not talk about the need for further tests, and appears ready to proceed. In a recent article (12) he states that "the grossly normal blastocyst" was not transferred to the patient for the single reason that she had recently undergone uterine surgery. He adds: "Otherwise, there was no discernible contraindication for a successful transfer in vitro [sic — he means, in utero] and continued development. This is scheduled for patients with ligated or excised fallopian tubes who may want a child, with the ova obtained by culdoscopy or laparoscopy."\*

The truth is that the risks are very much unknown. Although there have been no reports of gross deformities at birth after successful transfer in mice and in rabbits, the question of abnormalities has not been systematically investigated. No attempts have been made to detect defects that might appear at later times or lesser abnormalities apparent even at birth. In species more closely related to humans—e.g., in primates—successful in vitro fertilization has yet to be accomplished. The ability to produce normal young regularly by this method in monkeys seems to be a minimum prerequisite for use of the procedure in humans. The medical profession as a whole—and especially, professional societies of obstetricians and gynecologists—should press to see that this minimal requirement is met by all researchers.

But, even after normal young are produced in monkeys, we could not be certain that normal young would be produced in humans. There might be species differences in sensitivity to the physical manipulations or to possible teratogenic agents in a culture medium. Also, monkey experiments could neither rule out nor establish the risk of mental retardation for children resulting from experiments in humans. Unfortunately, as is often true, only humans can provide the test system for fully assessing the risks of using the procedure in humans.

Laboratory testing of the human embryos themselves, before transfer, cannot provide enough information about "normality," and might itself do damage. Gross abnormalities may be disclosed by ordinary microscopical observation. But ordinary microscopical observation can provide at best only a very crude measure of normality.

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\* The tone of the recent scientific articles and the reports of this research in the popular press suggest to the ordinary reader that a race may be on to the first embryo transfer. If such a race is on, it is likely that the swift will throw caution to the more sober, and will trust to luck that their victory in the race does not issue in a deformed or retarded child.

Most genetic tests cannot be done on a given embryo without damaging it; moreover, there are few genetic tests presently available for doing. Furthermore, damages might be introduced during the transfer procedure, even after the last inspection is completed. Conceivably, the manipulations might even make possible the implantation of some abnormal embryos that would have been spontaneously aborted if they had been generated under natural conditions.

In sum, there is at present no way of finding out in advance whether or not the viable progeny of the procedures of *in vitro* fertilization, culture, and transfer of human embryos will be deformed, sterile, or retarded. Even if we wished to practice abortion on all the misbegotten fetuses, we are not and will not be able to identify (by amniocentesis or other methods) many if not most of them. Neither can we count on "nature" to abort all of them for us.

The problem of risks and mishaps that accompany the experimental phase of this new technology provides a powerful moral objection sufficient to rebut the proposed implantation experiments. This moral objection should be widely shared, for it rests upon that minimal principle of medical practice, do no harm. In these prospective experiments upon the unconceived and the unborn, it is not enough not to know of any grave defects; one needs to know that there will be no such defects—or at least no more than there are without the procedure. The general presumption of ignorance is caution. When the subject-at-risk cannot give consent, the presumption should be abstention.\*

It may be objected that all new medical technologies are risky, and that the kind of ethical scrupulosity I advocate would put a halt to medical progress. But such an objection would ignore a crucial distinction. It is one thing to accept for yourself the risk of a dangerous procedure (or to consent on behalf of your child, even your intrauterine child) if the purpose is therapeutic. Some might say that this is not only permissible, but obligatory, in line with a duty to preserve one's own health or the health of one's children. It is quite a different thing deliberately to submit a child, born or unborn, to hazardous procedures which can in no way be considered therapeutic for him (and, as I shall argue shortly, is "therapeutic" for you only in that it "treats" your desires, albeit unobjectionable ones). This argument against nontherapeutic experimentation on children applies with even greater force against experimentation "on" a hypothetical child (whose conception is as yet only intellectual). One cannot ethically choose for him the unknown hazards that he must face and simultaneously choose to give him life in which to face them. This judgment could be set aside only under a strongly pronatalist ethic—much more pronatalist than Roman Catholicism ever was—which would hold that parents have either a preeminent duty or a preeminent right to have their own biologic child by whatever means.

#### EXPERIMENT OR THERAPY?

An attempt to produce a live baby by means of laboratory fertilization and culture certainly must be deemed "experimental" in the sense

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\* I would apply a similar argument to the case in which husband and wife are known to be carriers for the same severe, recessive, genetic disease. Such would-be parents would act responsibly by abstaining from procreation, and by adopting children instead. Whether the State and the law ought to compel this abstention is a wholly different question.

of being new and untested, full of uncertainties and unknown hazards. Yet the use of untested, potentially hazardous procedures can often be justified if the purpose is therapeutic (i.e., "nonexperimental"), and if the likely therapeutic benefits outweigh the likely risks. But is the purpose here therapeutic, or might it not also be labeled as "experimental" (i.e., nontherapeutic, or scientific) in this second sense as well? Clearly, the procedure is not therapeutic for the child generated. However, the first attempt to produce a live baby with a vitro fertilization will most probably be described as serving a therapeutic purpose for the parents—namely, the treatment of their infertility. But is this an accurate description? Is the inability to conceive a disease, or merely a symptom of disease? Can a couple have a disease? Does infertility demand treatment wherever found (e.g., in women over 70 or in virgin girls) or by any and all available means (e.g., by artificial insemination, by in vitro fertilization, by extracorporeal gestation, by parthenogenesis or by a sexual reproduction or cloning)?

Infertility is not a disease in the usual sense, but it can be a symptom of disease. It is not life threatening or crippling, nor does it lead to detectable bodily damage. To consider it a disease leads to a focus on an individual; yet infertility is a condition that is located in a marriage, in a union of two individuals. If it is any kind of disease, it is a "social disease." Even though the abnormality responsible is usually found in only one of the partners, their interaction is required to make the problem manifest.

More is at stake here than the correction of linguistic imprecision; the error in language is not innocuous. To consider infertility solely in terms of the traditional medical model of disease (or in terms of a so-called right of an individual to have a child) can only help to undermine, both in thought and in practice, the bond between child-bearing and the covenant of marriage. In a technological age, viewing infertility as a disease demanding treatment by physicians fosters the development and encourages the use of all the new technologies mentioned above.

Just as infertility is not a disease, so providing a child by artificial means to a woman with blocked oviducts is not treatment (as surgical reconstruction of her oviducts would be). She remains as infertile as before. What is being "treated" is her desire—a perfectly normal and unobjectionable desire—to bear a child. There is no clear medical therapeutic purpose that requires or demands the use of the new and untested technologies for initiating human life and that might possibly justify the unconsented-to use of a human subject for the benefit of others and a risk to himself.

#### IS THERE A HUMAN SUBJECT?

My use of the term "human subject," as applied to a prospective child, requires some justification. Who is the human subject of the fertilization, culture and implantation procedures? Do we mean to call a blastocyst a human subject? The questions are raised here can easily be distinguished from a similar question raised concerning abortion. With abortion, the moral question is when and whether one can justify killing the fetus; one of the underlying issues is whether the fetus is a human being or a potential human being worthy of

protection. Here, we are concerned with the possible harm inflicted upon the live, breathing children who come to be born after getting their start via a vitro fertilization and laboratory culture. The underlying issue is whether one can speak of such children and their ontogenetic precursors as "human subjects of experiments," especially when they are themselves the products of such experiments.

The issue can be clarified and possibly resolved if analogous harmful manipulations of the unborn are considered. A useful, though not perfect, analogy would be the deliberate administration of thalidomide or some other known teratogen to a pregnant woman. Whether the fetus is then "human" or not, the child it becomes would be an unwilling and unjustly injured victim of such unethical practice. More analogous would be the generation of a child through artificial insemination with sperm that had been deliberately irradiated or mutagenized. These examples, although hypothetical, serve to show that a child can be liberately injured before his birth, even coincidentally with his conception. If we ask who it is that was injured when the injury occurred, the answer must be, "the human subject," or at least, the "potential human subject," who is the prospective child. And if the child-to-be can be deliberately injured, he can be negligently injured, as he might be if he were the product of in vitro fertilization before the technic were shown to be free of risk.

This line of reasoning has already found its way into the law, and is likely to gain strength as the technologies for manipulating the unborn proliferate, and as we learn more about specific harmful effects of drugs and chemicals on the fetus. Indeed, legal actions claiming intentional and negligent wrongdoing have recently been brought by infant plaintiffs, against their parents or against doctors and hospitals, seeking damages for "wrongful life"—that is, life with inextricably linked handicaps such as illegitimacy or congenital syphilis (19). Although judges face grave policy questions in awarding damages to plaintiff in these cases (none have done so as yet), several of their opinions affirm that children can be and have been injured while unborn, and even at the moment of conception.

#### EXPERIMENTS WITH CHILDLESS COUPLES

Most of the scientific reports on human-embryo experimentation are strangely silent on the nature of the egg donors, on their understanding of what was to be done with their eggs, and on the manner of obtaining their consent. This silence is surprising in view of the growing sensitivity of the medical and scientific communities to the requirement of informed consent, and especially surprising given the kind of experiments here being performed. In a recent article in *Scientific American* by Edwards and Fowler (20), there is this solitary comment: "Our patients were childless couples who hoped our research might enable them to have children." From the report that they had hopes, we can surmise that they considered themselves to be patients. But so far as these experiments are concerned, they are only experimental subjects. The researchers owe us an account of how consent was obtained and of what the couples were in fact told.

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References at end of article.

Only one of the scientific articles, (14) that describing the use of laparoscopic surgery to recover human oocytes, tells us anything more about the persons used as experimental subjects, and about how they were informed: "The object of the investigations was fully discussed with the patients, including the possible clinical applications to relieve their infertility." Though welcome, this statement is incomplete. It does not tell us whether the couples were also informed that the much more likely possibility was that it would be future infertile women, rather than they themselves, whose infertility might be "relieved." At this stage of technical competence, the likelihood of failure must be made clear when consent to undergo laparoscopy is obtained.

It is altogether too easy to exploit, even unwittingly, the desires of a childless couple. It would be cruel to generate for them false hopes (e.g., by exaggerated publicity). It would be both cruel and unethical to generate hope falsely (e.g., by telling women that they themselves, rather than future infertile women, might be helped to have a child) to obtain their participation in experiments.\*

#### SOME PRACTICAL SUGGESTIONS

The arguments that I have developed, in this paper and elsewhere (18) (21) have led me to the conclusion that we need regulation of the technologic application of research in human reproduction (though not necessarily of the research itself). Some of the regulation can and should be done by scientists and physicians, and by their professional societies. Such intraprofessional self-scrutiny has been responsible for much of the progress made in recent years in improving the standards for human experimentation, for adequate drug testing and for care of laboratory animals. Regarding the particular issue of human experimentation raised in this paper, I suggest to my colleagues the following specific steps:

The first would be a profession-wide, self-imposed moratorium on attempts to produce new human children by means of *in vitro* fertilization and embryo transfer (and by other new procedures), *at least* until such time as the safety of the procedures can be assessed and assured.

The second would be initiation of critical, prospective studies in primates and other mammals to assess the "normality" of the young produced by artificial means.

The third would be establishment of intraprofessional bodies and forums to discuss and to evaluate critically work in mammalian and especially in human reproduction. Reports by such responsible professional groups could help to prevent the creation of inflated hopes and fears.

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\* That this may have already occurred is suggested by the following extract from a news report by Patrick Massey, of Reuters, that appeared in the Washington Post, March 3, 1970: "Dr. Patrick Steptoe, who heads the team of doctors working on the experiment, disclosed on television that he had extracted an ovum from a 34-year-old housewife and fertilized it with her husband's sperm. The woman, Mrs. Sylvia Allen, . . . said she hoped the fertilized ovum would be implanted in her womb in the next two to six weeks, meaning that the world's first baby conceived in a test-tube could be born by the end of 1970." The implantation was never performed.

Yet the questions of risk to the unborn and of informed consent are only a few questions among many that must be raised. Would the assurance of safety and normality provide a sufficient warrant for going ahead? Surely, there is more at issue than providing a child for an infertile woman. Once introduced for that purpose, laboratory fertilization can be used for any purpose. Indeed, the work described is a giant step toward the full laboratory control of human reproduction. What are the implications of this step, and of the others it makes possible (such as ectogenesis or cloning (22))—e.g., for the humanness of human procreation or for the human family? Should not the weighing of ethical and social considerations concerning both the widespread use and subsequent uses of the new technology enter into the decision to apply it for the first time?

These ethical questions point to a political question. Laboratory control of fertilization and embryonic development is a major departure in human procreation whose human consequences, both private and public, are likely to be profound. It is no mere ordinary medical (that is, therapeutic) advance. Therefore, one must question the wisdom of leaving the decision to go ahead for the private judgment of a team of physicians and scientists (whose judgment I am not now questioning), or even for the collective judgment of the medical and scientific community. Is this not a matter that deserves broader public deliberation and, in the end, might be one for public decision?

In the light of these remarks, I make the following additions to my list of specific proposals for physicians and scientists, and their professional societies:

Initiation of interdisciplinary discussion, both in and out of the Government, of the desirability of introducing the new technologies, and of the means for anticipating and minimizing the undesirable social consequences, if they are introduced.

Cooperation with lawyers, legislators, theologians, philosophers, humanists, social scientists and laymen in establishing ethical guidelines for the use of reproduction technology, and in providing for the proper legal safeguards for experimental subjects, including unborn children.

Convocation of international groups to consider desirable, necessary and feasible means of preventing follies and evils committed in the name of international competition.

Some, if not all, of these suggestions are likely to be unpopular, and some of them are not without their own dangers. But they should not be seen as harbingers of the bogeyman who goes around stopping research, but rather as suggestions for constructive and responsible steps that our growing power over human life obliges us to take. It should not be forgotten that our society already exercises considerable control over the rate of technologic development in this area, by means of its granting power and by the power that it confers on scientists and physicians. Thus, the question is not control versus no control, but rather what kind of control, by whom, and to what purpose. If doctors and scientists con-

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tinue to be shortsighted, if they fail to regulate themselves and to cooperate with other professions and groups with legitimate concerns in these areas, they can only expect society to react with more sweeping, immoderate and throttling controls in the future. One need only consider the likely public reaction if the first "test-tube-baby" turns out to be a monster.

Yet this concern for scientific self-preservation, for the right to experiment is insufficient. With our growing power to affect the lives of unborn children, through new technics for beginning life and coming technics for genetic manipulation, we scientists and physicians have a growing responsibility to that broader community to which we belong, the human race, and especially, to each human being upon whom we exercise our power.

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## APPENDIX 4

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