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Gene Therapy and Genetic Engineering: Frankenstein is Still a Myth, but it Should be Reread Periodically

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Biotechnology and the law are far removed from each other as disciplines of human intellect. Yet the law and my own discipline, genetics, have come together in many courtrooms concerning such matters as paternity, and they will continue to intersect with increasing frequency as the visions of 100 years ago become the reality of today. This article examines the implications of recent research for human genetic therapy and genetic engineering, and suggests some guidelines for legal regulation of genetic technology.

The following discussion derives from three premises which I view as basic: (1) that which is currently possible in genetic engineering, and in fact has already been done, is generally underestimated; (2) what may be possible in the near future is quite commonly overestimated; (3) regulation of the application of genetic technology is possible and will not be overwhelmingly complicated. I am not suggesting that this regulation will be an easy matter. It will, however, not be impossible, provided qualified representatives of the relevant disciplines work together rationally.

SOME BASIC GENETICS

Genetics as a discipline deals with what are best described as gut issues: what we are, where we came from and where we are going. In my teaching of general genetics, I repeatedly stress one basic principle: the mechanisms of genetics, from the level of a molecule, to that of a species, to that of all living material on earth, combine elements of profound conservatism with elements of the utmost flexibility. In other words, the mechanisms of genetics guarantee that what is “good” under a particular set of circumstances will be maintained; yet when what is “good” varies because of new circumstances, there is a capacity for rapid and adaptive change.

The study of genetics includes the scientific investigation of the storage, transmission, retrieval and utilization of information by living material. The scope of genetic study is tremendous. Before the work of this discipline on changing the genetic composition of man can be considered, however, the reader must understand some basic genetic concepts and terminology, particularly as they apply to man.¹

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1. The basic principles of Mendelian genetics are discussed in all genetics texts.
The Inheritance of Traits: Genotype and Phenotype

A human being is made up of many individual cells, perhaps a million million. Each cell, with noted exceptions, contains a body called a nucleus. Within the nucleus are located 46 chromosomes which can be grouped into 23 homologous pairs. These pairs are called homologs because the members of the pair appear to be identical under a microscope. Each homologous chromosome consists of the same linear sequence of genes, the particulate entities responsible for the potential transmission of a given trait from one generation to the next and for its development in an individual organism. The genotype of an organism is its entire genetic constitution, although one often speaks of the genotype with respect to only a small number of genes. A particular place or locus on a given chromosome and on its homolog is the site of a gene affecting a particular trait or phenotype of the organism. Thus, a person has two of each gene affecting a phenotype. The two genes may be identical to each other, in which case the individual is said to be homozygous for that gene or trait. However, genes occur in different kinds or alleles, and an individual who has two different kinds of alleles at a particular locus is said to be heterozygous. The phenotype of a heterozygote may be identical to one of the homozygotes or intermediate between them, depending on whether one allele is dominant. A dominant allele masks the trait determined by the other or recessive allele so that individuals who are heterozygous will be phenotypically identical to those who are homozygous for the dominant allele. In the absence of dominance, the phenotype of a heterozygote is intermediate to those of the two homozygotes. These principles are exemplified by two genetically determined disorders in man.

The operation of dominance can be seen in cystic fibrosis, a genetically determined disease that afflicts roughly one in every 1,500 persons. The disorder is caused by a recessive allele, so an affected individual must be a homozygote for that allele. Since this disease almost always kills prior to reproductive maturity, a child who has cystic fibrosis must have parents who are heterozygous for the disease. The dominant allele can be represented by an upper-case letter (C) and the recessive allele by a lower-case letter (c). In terms of gene content, each parent of a child with cystic fibrosis can be represented as (Cc). When these

2. Each human cell may contain as many as 100,000 genes.
3. For a description of known genetically determined disorders and their mode of inheritance see V. McKusick, MENDELIAN INHERITANCE IN MAN (3d ed. 1971) [hereinafter cited as McKusick].
parents produce sperm and eggs or *gametes* the number of chromosomes is precisely halved, with one chromosome from each homologous pair included in each gamete. The fusion of two gametes, one from each parent, at fertilization will restore the proper chromosomal number of 46. The distribution of homologous chromosomes during the production of gametes is random so that half of the gametes of a Cc individual will carry the C allele and half the c allele. Fusion of gametes at fertilization is also random, and, in a mating between the two heterozygous Cc individuals, this randomness would produce 25 per cent CC individuals, 50 per cent Cc and 25 per cent cc. Since the C allele is dominant, an average of 75 per cent of the offspring of two heterozygotes will be phenotypically normal and 25 per cent will be afflicted with cystic fibrosis. However, since these frequencies are based on averages of chance events, it is possible for two heterozygotes to have ten or more consecutive normal, or afflicted, children.

A lack of dominance is seen in the genetic disease of sickle cell anemia which, among residents of the United States, primarily afflicts Blacks. The allele which controls the synthesis of normal hemoglobin can be symbolized (H). The allele controlling the synthesis of sickle cell hemoglobin can be symbolized (h). Clearly, three genotypes are possible: HH, Hh and hh. The randomness of gamete production and fusion again predicts that a mating between two heterozygotes will produce 25 per cent HH, 50 per cent Hh and 25 per cent hh individuals. In this case, due to a lack of dominance (or more properly codominance), the phenotype of the heterozygote is intermediate to those of the two homozygotes. Although heterozygotes (Hh) suffer only a mild anemia, recessive (hh) individuals die from severe anemia before reproductive maturity.

4. The distribution of non-homologous chromosomes with respect to each other is also random. Therefore, the distribution of genes on non-homologous chromosomes is random. However, each chromosome contains many more than one gene, and genes located on the same chromosome are linked, *i.e.*, their distribution during gamete formation is nonrandom. Morgan, *Random Segregation Versus Coupling in Mendelian Inheritance*, 34 SCIENCE 384 (1911). See also Levine, supra note 1, at 90-112. Linked genes tend to be inherited together, although a mechanism does exist for reshuffling such genes. Until quite recently, it has been difficult to determine what genes of a human being are linked. Newer technology has made such determinations simpler. Ruddle, *Linkage Analysis in Man by Somatic Cell Genetics*, 242 NATURE 165 (1973). This information should have a clear effect on counseling and other uses of genetic information.

5. Of course, the genetic composition of an individual is not random but is dependent on the nature of the genes carried by that individual's parents. However, the transmission of genes from parent to child is determined, in large part, by chance.

6. One slight variation of this general, and relatively simple, pattern of inheritance is found in sex-linked inheritance. Morgan, *Sex Limited Inheritance in Drosophila*, 32 SCIENCE 120 (1910). See also Levine, supra note 1, at 79-89. A classical example of a disease that is genetically determined and inherited in a sex-linked manner is
Having examined a few basic genetic principles, let us turn now to the mechanism by which genetic information is carried. It is probably universal knowledge that genetic information is carried by molecules of deoxyribonucleic acid (DNA). The molecule is composed of two half-molecules, or strands, which are precisely complementary to each other.

In order to avoid one common point of confusion, it must be stated explicitly that the two strands of a DNA molecule do not represent the two alleles of a gene. The two alleles are located in two different DNA molecules, and each molecule is double-stranded. It was originally demonstrated by Meselson and Stahl that the DNA molecule is duplicated in a "semi-conservative" manner when a cell division takes place. The two half-molecules separate, and each acts as template for the synthesis of a new, complementary half-molecule. The result is two molecules, each identical to the original one and each composed of one "old" and one "new" strand. This mechanism of molecular duplication provides for the precise transmission of that information contained in the DNA molecule from one cell generation to the next.

The majority of DNA seems to control the production of pro-

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7. Demonstration of the molecular identity of the carrier of genetic information involved many elegant experiments which are not really germane to this discussion. See Avery, MacLeod & McCarty, Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Deoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III, 79 J. Exp. Med. 137 (1944) [hereinafter cited as Studies]; Hershey & Chase, Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage, 36 J. Gen. Physiology 39 (1952).


teins in the cells. The sequence of subunits within a DNA molecule ultimately determines the sequence of subunits in a protein. The subunits of a protein are amino acids. The sequence of these amino acids is so important in the maintenance of life functions that, in some cases, just a small change in the amino acid sequence of a single protein can kill a person. If an individual has normal, adult hemoglobin, one part of the hemoglobin molecule within his cells contains the amino acid called glutamic acid. In a heterozygote for sickle cell anemia, roughly half of these molecules contain glutamic acid at that particular place and half contain a different amino acid, valine. In individuals who are homozygous for the sickle cell gene, all hemoglobin molecules contain valine at this particular place. This change in one amino acid in the protein is caused by only a single change in a DNA molecule, yet it is lethal.

Natural and Artificial Selection

An individual organism with a given genotype and phenotype exists in a given environment. Each of these factors has its effect on the organism. Darwin’s synthesis of the theory of evolution suggests that in each environment some genotypes will be more fit than others, and that natural selection will lead to an increased frequency of more fit individuals and a decreased frequency of those less fit. This selection operates at the level of a population or species and will not necessarily eliminate all of the less fit individuals from the population. More often, the frequency of less fit individuals is reduced by their lower rate of reproduction or lower reproductive fitness. This reduced fitness also leads to a decrease in the frequencies of those genotypes found in the less fit individuals. Eventually, through the mechanism of natural selection, an equilibrium is established in a population with the frequencies of the various alleles in a steady state. If an environmental change occurs or the population migrates to a new environment, the population will be subjected to new selective pressures and a new equilibrium of gene frequencies will be established.

It is reasonably clear that natural selection applies to human popula-

14. Although the process of selection was not stated systematically until Darwin’s time, its basic principles have been known for millenia. These principles have been utilized in the practice of artificial selection for agricultural improvements.
A somewhat complex example is presented by sickle cell anemia which, as discussed above, is caused by a variant form of human hemoglobin inherited in a pattern of codominance. Sickle cell heterozygotes, who can be detected simply, have a mild anemia which causes little or no distress except at high altitudes where the reduced oxygen-carrying capacity of the blood produces some difficulty. However, individuals homozygous for the sickling gene have severe anemia, and almost invariably die prior to reproductive maturity. Since the gene for sickle cell hemoglobin is lethal in homozygotes, one would expect it to be reduced to a very low frequency in the population by natural selection. This is the case in some human populations but not in others.

The probable basis for the maintenance of the gene is suggested by the historical geographical distribution of populations with high frequencies of the disease. These populations occur in, or are derived from populations that have occurred in, regions of high endemic malaria. Individuals who are heterozygous apparently have a higher resistance to malaria than do individuals who have completely "normal" hemoglobin. Thus, while selection operates against the sickle cell gene by the removal of homozygotes from the reproductive population, it also operates in favor of the gene by the increased fitness (due to malaria resistance) of heterozygotes as compared to dominant homozygotes.

The attainment of a genetic equilibrium through natural selection depends on the presence of random breeding among members of the population. Where breeding is nonrandom, the genetic composition of the population reflects the effects of artificial selection. Artificial selection has long formed the basis of improvements in agriculture. If plants or animals with desired properties are encouraged to mate with each other, and others are discouraged or prevented from mating, over a period of time the majority of the population will come to have the desired properties.

There is also artificial selection in human populations since matings

17. The maintenance in a population of the allele leading to synthesis of sickle cell hemoglobin provides an excellent demonstration of two principles. The first concerns determination of what is a "good" gene. The second is the fact that, while genes affect the phenotype of a single individual, selection acts on a population of individuals. The sickle cell hemoglobin gene clearly is not a "good" gene for a homozygous individual in any environment or for a population which inhabits an area where malaria is not endemic. However, it is a "good" gene to maintain in a population of individuals living in a malarial environment. The benefit of having the sickling gene maintained in the population, of course, accrues to the population as a whole and not to the homozygous individuals who will be produced (and die) as a result of the maintenance of this gene.
between human beings do not occur at random. The human species is essentially world-wide in distribution, but geographical barriers prevent matings between certain individuals. Probably even more important in producing nonrandom mating are the social barriers raised by various groups. Religious, ethnic, social and economic classes commonly have strict regulations concerning who may mate with whom. Outbreeding is enforced in some cases and inbreeding in others. Either of these will result in nonrandom mating and artificial selection. If a population is relatively small and inbreeding is enforced, such as by permitting only those marriages which are between members of the same race or religion, the frequency of homozygous individuals can increase at a very rapid rate. Such selection can be considered to be artificial since it results from imposed cultural preferences rather than from natural environmental conditions.

**Genetic Technology and Therapy**

Let us now examine some developments in controlling the genetic traits of human beings, consider the technological limitations on such controls and raise the legal and ethical problems presented by those control methods that are now, or may later become, possible.

**Detection of Genetic Diseases**

Methods have been developed for the detection of many genetic diseases. Such detection makes possible treatment of afflicted adults and prevention of the birth of afflicted children. Persons who are heterozygous for sickle cell hemoglobin can be detected by a simple technique. In several communities large scale screening programs have been developed with state and federal support. In such a program in Hartford, Connecticut, participation was voluntary and permission for screening children was requested of 5,000 parents. Consent was obtained for the testing of 3,456 children. Initial testing indicated that 301, or about ten per cent, of the tested children were heterozygotes. From a genetic point of view it is very useful for an individual without apparent sickle cell disease symptoms to know if he or she is heterozygous for the disease. It would enable that person to determine the chance of producing afflicted offspring. If only one member of a couple carries the sickle cell allele, then, barring a highly


20. *Id.* at 284. Retesting of these children by a second method indicated that four of the initial tests were in error. *Id.*
unlikely mutation, the couple will not have a child with severe sickle cell disease. If both members of a couple are heterozygotes, the chance that any given child will be afflicted is 25 per cent. Such a couple could be made aware of the danger and decide whether not to marry, to marry and not have children, or to marry, reproduce and take the chance of producing an afflicted child. Screening can also be valuable in early detection of individuals with genetic diseases to allow treatment of the disease where such treatment is available.

Detection of genetic diseases in embryos by amniocentesis is now possible in some cases. A sample of amniotic fluid which contains some fetal cells is removed. These cells are grown in cell culture, and, after sufficient cell division has taken place, analyzed for chromosome content. A variety of genetic diseases can be detected. If a genetic disease is found in the fetus, the parents can decide whether to bear the child or have an abortion. However, amniocentesis, like any surgical procedure, is not without its dangers and should not be performed without adequate justification. In my mind, a 25 per cent probability of a severe genetic defect is sufficient to justify amniocentesis.

It is not yet possible to use amniocentesis for the detection of genetic diseases that are not reflected in abnormally shaped chromosomes. For example, sickle cell anemia is expressed only in the hemoglobin of red blood cells and its presence or absence cannot be determined from an analysis of the nuclei of fetal cells in the amniotic fluid. Fetal red blood cells must be examined. This blood must be taken from the fetus itself since no fetal blood is present in the amniotic fluid. However, in order to remove blood from the fetus, it is necessary to know the precise fetal position if damage is to be avoided. It is not now possible to determine the precise position, although this problem can presumably be eliminated.

Even where there are no technological barriers to detection of genetic diseases, it is necessary to consider what use should be made of the information obtained. First, if heterozygotes can be detected, should a high risk group be provided with, or compelled to submit to, screening? If such compulsion seems unattractive, note that there is precedent for compulsory biological testing of people. Most states already require a premarital blood test to detect syphilis. Indiana requires that all newborn babies be tested for a genetically determined disease called phenylketonuria.

21. A mutation is a change in a gene from one allele to another.
22. E.g., CAL. CIV. CODE § 79.01 et seq. (West 1954); COLO. REV. STAT. ANN. § 90-1-4 (Supp. 1971); ILL. ANN. STAT. ch. 89, § 69 (Smith-Hurd Supp. 1973); IND. ANN. STAT. § 31-1-1-7 (Code ed. 1973); N.Y. DOM. REL. LAW § 13-a (McKinney 1964); OHIO REV. CODE ANN. § 3101.05 (Page Repl. 1972).
Second, if it is determined that a couple are both heterozygotes, and therefore that one-fourth of their children may be afflicted with a fatal genetic disease such as sickle cell anemia, should they be discouraged from or forbidden to reproduce? Restrictions on reproduction are clear limitations on individual freedom. Yet they might be in the couple's best interest since the emotional stress from the death of a young child and the cost of medical care prior to death would be avoided.  

Third, if a homozygous, afflicted child is born, should efforts be made to treat the individual? Several considerations are important here: the effectiveness or degree of normality of the afflicted individual, the length of time that maintenance on a therapeutic regimen is possible, and the cost of treatment.

Finally, the possibility of treatment raises a fourth problem that is genetic and, to me, the most important. What will be the effect upon the genetic pool if the abnormal traits associated with genetic defects are treated? Untreated individuals with many genetically determined disorders, such as sickle cell anemia, usually die before reaching reproductive maturity. The relative frequencies of the normal and mutant alleles are kept in equilibrium by natural selection. If an effective treatment for genetically determined disorders were developed, homozygous, afflicted individuals would survive and reproduce. This would produce artificial selection imposed by technology, and, over a period of time, the frequency of the defective gene would increase. I know of few geneticists who would oppose treatment of the symptoms, or phenotype, of a person with sickle cell anemia or any other genetically determined disorder. However, many would be concerned about the effect of the reproduction of such therapeutically maintained persons. The effect can only be an increase in the frequency of the defective allele and a corresponding decrease in the frequency of the normal one. Although some geneticists feel the rate of increase will be so slow that is is unimportant, others feel any such increase in the frequency of detrimental alleles is significant and steps should be taken to discourage reproduction by afflicted persons. Still others, such as the late H. J. Muller, hold more extreme views and maintain not only that individuals with detrimental alleles be prevented from reproducing, but also that individuals with desirable traits be encouraged to do so.

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24. The argument for pre-conception restrictions is weaker in the case of those disorders which can be detected in the fetus prior to birth.
26. See, e.g., Muller, Further Studies Bearing on the Load of Mutations in Man, 6 Acta Genetica et Statistica Medica 157 (1956); Muller, Genetic Principles in Human Populations, 113 Am. J. Psychiatry 481 (1956); Muller, The Guidance of Human Evolution, 26 Biology & Human Affairs 1 (1961) [hereinafter cited as
It is my opinion that the law and the sciences must begin to co-operate effectively to anticipate these and other problems that will be created by the use of genetic technology and ensure that our society is ready to regulate such use. Those matters which will confront us in the near future will be among the simplest to resolve and will provide a base of experience with which to resolve the more difficult matters of the more distant future. However, even application of the simple technology that is presently available can lead to many problems.

For example, we must be aware that while even voluntary screening programs have many potential benefits, such programs may also produce unpleasant side effects. Parents who have a child with a genetic disease may feel they are personally responsible for the defect. A social stigma seems to attach to persons who are heterozygotes for genetically determined disorders. It has been suggested that identified heterozygotes experience job discrimination and have difficulty in obtaining life and health insurance. In my opinion, all of this is nothing short of absurd. The intent of those who propose screening programs is not discrimination, but amelioration of an unpleasant situation. Their motives are humanitarian. If this technology, as well as the more sophisticated techniques that are discussed below, is to be applied, everyone must understand the genetic basis of such disorders and the means used to detect and treat them. Moreover, there must be widespread understanding of the fact that all people are equally subject to genetic disease because all are equally subject to natural selection and the randomness of mutation, gamete formation and the union of sperm and egg. It must be made clear to everyone that there is no culpability for genetic disease since its occurrence is determined by matters over which we have no control. I suggest that such understanding could be promoted by modifying the content of the genetics curriculum now taught in most secondary schools to include the social issues raised here.

Unless we use genetic technology in a rational manner, the problems of its use will increase. I believe that any technological development should not be applied until our society is intellectually prepared to understand its meaning. In short, I would urge us to move slowly in applying genetic therapy and to be sure we know what we are doing before we do it.


Muller proposed not only the encouragement of natural reproduction of fit individuals but also the use of artificial methods of reproduction. The latter includes methods presently available, such as sperm banks and artificial insemination, and methods which may soon become available, such as in vitro fertilization, embryo transplantation, frozen storage of embryos and cloning.

27. Culliton, supra note 19.
Imposed Artificial Selection

A technique that could be used to intentionally alter the genetic composition of a human population is imposed artificial selection. Matings between certain individuals could be encouraged and those between others discouraged or even forbidden. Enforcement measures are easy to envision. Such imposed selection would change the total gene content of the human species. Therefore, whenever the matter is discussed certain questions always arise: Who should decide what to select? Who should control and who should control the controller? Who should decide what is a good gene and what is bad? Does "good" mean good for the individual or for a population? Any decision concerning what genes to select is a value judgment. I cannot say how to make that decision; I am not even convinced that it should be made. Although there is potential benefit for the human race if we assume control of the direction of our evolution, imposing selection for any purpose other than the elimination of clearly defective genes is fraught with danger. Nature is far wiser than we are. Let us treat the symptoms of genetic diseases and attempt to reduce the frequency of clearly defective genes. Beyond that, let us permit natural selection to act freely.

Transformation and Transduction

The phenomena of transformation and transduction, first observed in bacterial research, could have a significant impact on human gene therapy. Transformation and transduction are parasexual phenomena which were important in early research on the molecular identification, organization and regulation of genetic material in bacteria and bacterial viruses. Similar phenomena are now being described in higher organisms and are proposed as potential approaches to gene therapy. Transformation is a process whereby genetic material from one type of bacteria directs a genetic change in a second type of bacteria when both types are present in the

29. See note 15 supra & text accompanying.
30. We have not been able to significantly interfere with nature long enough to have rigorous documentation of the truth of this statement. But can anyone rationally believe that a "Nature" which generated living material is not wiser than man who has only managed to poison his planet virtually to the point of death?
31. A parasexual phenomenon is a process that has the net effect of sexual reproduction in that it produces recombinant genotypes (an individual with a genetic composition different from that of the individual or individuals from which it is derived) without any mating process or physical contact between the individuals involved.
same host organism. In transduction, genes are transferred from one bacterium to another by a virus. Both transduction and transformation make it possible to alter the genotypes of bacteria. Will it be possible to use a similar technology to specifically alter the genotypes of higher organisms, including humans? I think the answer to this question is a guarded "probably". However, I believe that the therapeutic value of such techniques will be minimal for many years and that it would be inappropriate to suggest that we will ever be able to routinely cure genetic diseases by these methods.

A phenomenon essentially like transformation has already been produced in the fruit fly, *Drosophila melanogaster.* Fox and Yoon de-

32. Some early experiments by Griffith on the molecular identity of the genetic material illustrate the phenomenon of transformation. Griffith, *The Significance of Pneumococcal Types*, 27 J. Hygiene 113 (1928). There are strains of pneumococci (Type I) which are virulent and cause pneumonia in mice infected with them. When grown on an agar plate, a type of artificial culture medium, these virulent bacteria form a smooth colony. Mutant strains of pneumococci (Type II) exist which do not cause pneumonia in mice; these are nonvirulent and form rough colonies when grown on an agar plate. Griffith demonstrated that injection of mice with virulent Type I bacteria produced pneumonia and death. Injection of nonvirulent Type II bacteria did not cause pneumonia, nor did injection of heat killed Type I or heat killed Type II. However, if a test animal was simultaneously injected with heat killed Type I pneumococci and live nonvirulent Type II bacteria, pneumonia developed and death resulted. Furthermore, at autopsy virulent Type II bacteria which formed smooth colonies on agar plates were recovered. This was a stable line of bacteria; it reproduced in type over many generations. The control experiments eliminated any possibility that mutation was responsible for this change. It is this process which results in a permanent genetic change in a bacterial strain that has been termed *transformation.*

Clearly, something is present in the heat killed virulent Type I bacteria which can direct a genetic change in the live nonvirulent Type II bacteria. That something is called the *transforming principle.* Experiments by Avery, McCarty, and MacLeod showed that the only molecular portion of the Type I bacteria with any activity as a transforming principle was DNA. *Studies, supra* note 7.

33. Transduction may occur when a bacterium is infected by a bacterial virus (also called a bacteriophage or simply phage). Upon infection of a bacterium by a phage, one of two courses of events are possible. Which course is followed depends on the types of bacterium and phage involved. The first, and more frequent, course is a lytic interaction. The virus takes over the bacterial metabolism and uses it to synthesize copies of the viral genetic material, or genome, at a high rate. These genomes are then packaged within protein coats to form new viruses. Ultimately, the bacteria are lysed, or caused to burst, and a large number of progeny viruses are released.

The second possible course of events is a so-called "lysogenic" interaction, or lysogeny, in which the injected viral genome physically inserts into the bacterial genome and replicates in synchrony with it. Lwoff, Siminovitch & Kjeldgaard, *Induction of Bacteriophage Lysis of an Entire Population of Lysogenic Bacteria*, 231 Comptes Rendus Hebd. Séances Acad. Sci. 190 (1950). However, on occasion, this inserted phage genome, called a "prophage," can break loose from the bacterial genome, resulting in the rapid reproduction of the virus and lysis of the host. When the prophage breaks loose from the bacterial genome, either spontaneously or under the influence of an agent such as ultra-violet light, it may incorporate a part of the host bacterial genome into its own structure. This host bacterial genome may then be transferred to a second bacterium resulting in *transduction,* or the transfer of information from one bacterium to another by a virus vector.

34. Fox & Yoon, *DNA-Induced Transformation in Drosophila: Locus—"
veloped a treatment technique whereby embryos from one Drosophila strain were caused to incorporate DNA extracted from flies of another Drosophila strain. The flies that were used as DNA donors were normal, or wild type, flies with red eyes and gray bodies. The embryos were from a mutant strain and would have all developed into mutant flies with white eyes and yellow bodies if left untreated. Both eye color and body color are genetically determined in Drosophila. Most of the treated embryos developed into mutant, white-eye, yellow-body flies. But in a small percentage, less than one per cent, patches of red appeared in the eyes and patches of gray on the bodies. Parts of these flies had been transformed by the DNA from wild type flies. However, in no case was a whole-body transformant isolated. All transformed individuals were mosaics—i.e., parts of their bodies were normal and part mutant. Furthermore, the part of the body which was transformed was apparently random. It is significant that when flies with apparently transformed testes or ovaries were mated, none of the progeny were whole body transformants, thus indicating that there was not a complete transformation of the reproductive cells of such flies. Hence, a sort of transformation is possible in Drosophila, but it is incomplete and essentially random.

Use of such technology on a human embryo carrying a genetically determined disorder will be even more difficult than its use on fruit flies. In the case of Drosophila, the mutant nature of the embryo was known because flies with known homozygous genotypes were forced to mate. The genotype of the embryo to be treated was known from the time of conception. This would not be the case with an embryo produced by two human beings. Suppose that both members of a reproductive pair are heterozygous for sickle cell anemia or any other genetic disease. There is a 25 per cent probability that they will produce a homozygous, afflicted child. Before treatment of the fetus could be initiated, its genotype would have to be determined. Not only is that impossible in many cases, but even where it is possible, the genotype cannot be determined until well into pregnancy. By this time, the fetus consists of millions of highly differentiated cells. Since not all genes that are present are expressed in all cells, it is necessary to treat only those cells that actually express the defective gene, i.e., only treatment of the appropriate target organ is required. But even location of the appropriate target organ and

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35. Fox & Yoon, supra note 34; Fox, Yoon & Gelbart, supra note 34.

36. The fruit fly has been used extensively in genetic research and thousands of mutant strains are known.

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treatment to transform a sufficient number of target cells so that a normal phenotype could be sustained would no doubt be difficult. Moreover, there are nontechnological problems in the application of this process. No one is particularly concerned if the Drosophila which develops from a transformed embryo is a monstrosity; one could simply kill it or permit it to live in order to see if it were fertile and what its progeny might be like. The legal and ethical implications of a similar result with a treated human embryo are somewhat more disquieting.

The prediction that transduction may be used in human genetic therapy is based on a number of experiments. Two sets of such experiments illustrate the principles and problems involved. The first involves the transfer of a sugar-producing gene from the common *Escherichia coli* bacterium to human cells which are defective because they lack that gene.\(^7\) This transduction has only been accomplished with human cells in cell culture, and it is not yet clear whether it could be done with cells in a living person or in an embryo. Furthermore, not every cell in the culture was altered, so the therapeutic use of this technology is subject to the same limitations presented by the mosaic nature of the transformation of Drosophila embryos.

A second set of transduction experiments on human material involved the transfer of a gene controlling arginase production from a rabbit to man by a virus.\(^8\) Arginase is a blood serum enzyme that is

37. A phage called lambda infects the common *Escherichia coli*, or *E. coli*, bacteria and its viral DNA may be inserted into the genome of the host bacterium, *i.e.*, lysogeny may be established. See note 33 supra. This phage always inserts adjacent to a gene involved in metabolism of the sugar galactose. Some of these lambda phages then incorporate the *E. coli* gene for galactose metabolism and are able to transfer that gene in transduction.

In man there is a genetically determined disorder, galactosemia, in which the affected individual lacks a particular protein and is therefore unable to metabolize galactose. The protein which is missing in a person with galactosemia is coded for by that gene in *E. coli* adjacent to the site of phage lambda insertion.

The lambda transducing phages which have incorporated the *E. coli* gene for galactose metabolism have been isolated and used to infect human cells from a galactosemic individual in cell culture. Merril, Geier & Petricciani, *Bacterial Virus Gene Expression in Human Cells*, 233 *Nature* 398 (1971). Some of the human cells were transduced from galactosemic to normal. *Id.*

38. The transducing virus for the arginase gene is the Shope virus. This virus, named after its discoverer, causes a skin cancer in certain rabbits, Beard, Bryan & Wyckoff, *The Isolation of the Rabbit Papilloma Virus Protein*, 65 *J. Infectious Diseases* 43 (1939), but is apparently not tumor producing or otherwise detrimental in man. However, people who are infected with Shope virus develop abnormally high levels of blood serum arginase. Rogers has demonstrated reasonably conclusively that Shope virus incorporates from its original host that gene which codes for arginase. Rogers, *Change in the Structure of Shope Papilloma Virus-Induced Arginase Associated with Mutation of the Virus*, 134 *J. Exp. Med.* 1442 (1971). The gene is then expressed in the infected person by the production of elevated levels of the enzyme. Clearly, arginase production by this method in persons with arginemia would be of therapeutic value.
essential for the proper metabolism of the amino acid, arginine. Some individuals have a genetic disease, arginemia, in which they lack arginase. This defect is lethal early in life because arginine metabolism is intimately involved in the necessary elimination of nitrogenous wastes. The gene apparently has been transferred to normal individuals by the virus. More significant from the point of view of gene therapy are the reports that intentional infection with the virus has led to arginase production in individuals with arginemia.

There are other examples of genetic changes brought about in mammalian cells by treatments involving transduction. In most cases a virus vector is used to transfer DNA from one source to another. We already have the ability to isolate some genes and synthesize others. It has been suggested that treatment of many genetically determined diseases by transduction of isolated or synthesized genes will soon be possible. However, some scientists, including myself, are more cautious about such predictions. The problems to be surmounted are great as are the potential dangers. One difficult technical problem is the delivery of the gene to the proper target organ. Consider the example of Tay Sachs disease which affects primarily the postnatal development of nervous tissue. A homozygous individual almost invariably dies during the first year of life. The molecular basis of this disorder is known, and perhaps a gene therapy could be developed for this disease, although such treatment seems improbable for some time to come. Assuming the normal gene could be isolated or synthesized, it would have to be delivered to the target organ, the nervous tissue. A virus vector could be proposed as a delivery vehicle, but the kinds of viruses which infect nervous tissues, e.g., polio and rabies, are themselves dangerous. One would have to be certain that the ability of the delivery virus to cause disease was irreversibly eliminated. It is really not desirable to cure a genetic disease by causing an infectious one. Moreover, all of the changes induced so far have involved the replacement or masking of defective genes which are recessive. However, some mutant alleles are dominant over their wild type alleles. Since recessive genes have no phenotypic effect when their dominant alleles are present, there seems to be little hope of correcting the effects of a dominant mutant, such as that which produces Huntington's Chorea, by adding some recessive wildtype genes to the genome.

All these proposed gene therapies fail to produce genotypic changes for the whole body. If such a therapy corrects the phenotype of the organism and even the genotype of some cells, but fails to correct the genotype of the gamete-forming tissues, the therapy can only increase the frequency of the abnormal gene. The resulting increase in the frequency of the defective gene probably would be slow, but it would in-
crease as the result of artificial selection. This could only increase the use of gene therapy, the genetic load of the species and ultimately the fiscal and emotional price which society must bear. Therefore, I believe that we should not attempt any gene therapy except under the following circumstances: if I am dying from a disease, genetically based or not, and you have an experimental therapeutic procedure which might save my life, I am yours to experiment with upon my consenting to the therapy. However, having saved my life, you have the right to require me to submit to sterilization if the disease was genetically determined.  

In Vitro Fertilization and Embryo Transplantation

Some fertile women are unable to conceive due to a defect in the structure of their reproductive organs, such as a block in a Fallopian tube. The sterility of such a woman might be overcome if ova could be removed from her ovaries at the proper time, fertilized outside of her body, maintained in vitro until her uterus was ready for implantation and then inserted into the uterus. Such a procedure has been accomplished with mammals. Furthermore, there is a report of a successful embryo transplant in a human being, although the pregnancy is reported to have been terminated very soon after transplant. This report, and other well-documented publications, convince me that such reproductive technology will be routinely available for human beings in the very near future, if it is not already at hand.

Other research has examined the possibility of embryo transplantation—i.e., the transplanting of an embryo from the uterus of one female to that of another. All that is required is that the embryo be isolated without damage and implanted in a uterus in the proper condition. The procedure has been successfully accomplished in experiments using several different mammals. The recent work carried out by Whittingham and his coworkers is especially interesting because it adds a new dimension of

39. Friedmann and Roblin have proposed guidelines which they believe should be met before gene therapy is attempted. Friedmann & Roblin, Gene Therapy for Human Genetic Diseases?, 175 SCIENCE 949 (1972). Upon first reading, these struck me as incredibly conservative, but I must acknowledge that I have since become far more conservative myself concerning these matters.


41. Rorvik, The Test-Tube Baby is Coming, LOOK, May 18, 1971, at 83. Many scientists place little credence in this report, probably due to the place of publication, Look Magazine. In biology, however, one does hear rumors and reports as “personal communications” which suggest that much unreported work is going on in the area of in vitro fertilization and embryo transplants. Cf. Shettles, Human Blastocyst Grown in vitro in Ovulation Cervical Mucus, 229 NATURE 343 (1971) (reporting the successful in vitro fertilization of of a human egg and subsequent embryonic growth in vitro) [hereinafter cited as Shettles].
technology and complexity. Whittingham’s group recovered mouse embryos at the two-to-eight-cell stage of cell division following fertilization. These embryos were then frozen to temperatures as low as \(-269^\circ C\), just four degrees above absolute zero, and stored for as long as eight days. The thawed embryos were then implanted in foster mothers. Sixty-five per cent of the transplants were successfully received by the foster mothers, and almost 50 per cent of the implanted embryos developed into normal, living mice. Thus, not only can mouse embryos be transplanted from one animal to another, but they can also be frozen in between. It seems certain that similar technology could be worked out with respect to human beings. In fact, it may not be necessary to isolate an embryo from one female and transplanted it into a foster mother. Instead, embryos produced from the \textit{in vitro} fertilization of human ova could be used. There is no apparent technological reason why these embryos could not be implanted in the uterus of any receptive female.

**Cloning**

A clone is a number of cells which are all derived from a single parental cell by a series of cell divisions. All the cells of a clone are genetically identical. It is a simple matter to clone a microorganism since a single cell can be isolated and used as the starting material for an entire population. It is also possible to clone human cells in cell culture. But I use the concept of cloning in the somewhat different sense of an artificial means of producing a person. For such cloning, an unfertilized human ovum would have to be isolated, the nucleus would have to be either mechanically removed or functionally incapacitated, and a nucleus transplanted into an isolated enucleated oocyte, and the oocyte would have to be activated and cultured in vitro. It seems certain that such technology could be worked out with respect to human beings. In fact, it may not be necessary to isolate an embryo from one female and transplanted it into a foster mother. Instead, embryos produced from the \textit{in vitro} fertilization of human ova could be used. There is no apparent technological reason why these embryos could not be implanted in the uterus of any receptive female.

43. Just how normal they were can be seen on the cover photograph of \textit{Science}, Oct. 27, 1972.
44. See Shettles, supra note 41. Although Shettles reports that the development of the transplanted embryo was intentionally terminated shortly after implantation, there is no reason to suppose that development could not have continued.
45. These are mitotic, rather than meiotic divisions, \textit{i.e.}, they are the same type of cell division involved in normal animal growth rather than the type involved in gamete formation.
46. Except for the gametes, a human being is a clone because all of its cells are derived from a single fertilized ovum. Moreover, identical twins, those derived from one fertilized ovum, are a clone.
isolated from another person would have to be implanted into the ovum. The resulting zygote would be genetically identical to the donor of the nucleus—a younger identical twin.

Cloning of this nature has been accomplished in some higher animals. However, it has been done not for the purpose of developing an artificial reproductive technology, but rather to investigate some basic problems concerning development and differentiation.\(^{47}\) Nuclei were removed from unfertilized frog eggs and replaced with nuclei taken from embryonic frogs or tadpoles. Some of these developed into mature adult frogs which were apparently normal. All such frogs that developed from nuclei taken from the same developing embryo were genetically identical and were members of a clone.\(^{48}\)

Cloning is literally from the Brave New World.\(^{49}\) When people hear of the concept and learn that the procedure has been accomplished they often disregard the fact that it has been accomplished in amphibia (frogs)—not in mammals. They tend to be so enthusiastic or so distressed about the possible uses and abuses of cloning that they fail to

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47. All cells of an organism, except the reproductive cells, have the same number of chromosomes. The chromosomes of all cells look alike, and all contain the same amount of DNA. Yet it is clear that there are very diverse types of cells in a complex organism such as a human being. The diversity is due to the fact that some genes are expressed in some cells and not in others. One current problem in genetics is to understand how such differential gene expression occurs. A related problem is to understand how some genes become permanently inactive during differentiation, or formation of the structural parts of an embryo. Such permanent inactivity of the genes is evidenced by observations that certain types of structural development that occur in an embryo are no longer possible in an older organism. If a person sustains a major cut, a scar will form as it heals. Sufficient damage has been done to the skin that precise repair is impossible; the person has lost the ability to form large areas of skin. Similarly, if a finger, toe, or limb is amputated, all that is left after healing is a stump. A human being past the embryonic stage is genetically incapable of differentiating a new limb.

In an attempt to approach these problems, R. W. Briggs and T. J. King initiated a technically difficult and very informative series of experiments. Briggs & King, *Transplantation of Living Nuclei from Blastula Cells into Enucleated Frogs' Eggs*, 33 Proc. Nat'l Acad. Sci. 455 (1952). They developed techniques of mechanically removing the nucleus from an unfertilized frog egg. Diploid nuclei, taken from developing embryos at various stages of differentiation, were then transplanted back into the enucleated ova. In the initial work of Briggs and King, the donor nuclei had to be derived from embryos at a relatively early stage of development in order to be effective in cloning. In more recent work by Gurdon using a different species of frog, diploid nuclei from the intestine of a tadpole transplanted into enucleated ova were found to support development of apparently normal frogs. Gurdon, *Nuclear Transplantation in Amphibia and the Importance of Stable Nuclear Changes in Promoting Cellular Differentiation*, 38 Q. Rev. Biol. 54 (1963) [hereinafter cited as Gurdon]. Work currently in progress in Dr. Briggs' laboratory is extending the technology of cloning even further, according to a personal communication between this author and Dr. Briggs.

48. See note 47 supra.

49. A. Huxley, Brave New World (1932).
realize that it is technically much easier to work with amphibian than with mammalian material. Amphibian ova and their nuclei are much larger than those of mammals and therefore are much easier to manipulate. Moreover, even in the work on amphibia, the frequency of successful cloning is low. Many ova which are enucleated and receive a nuclear transplant either do not develop or develop abnormally. Another technical difficulty with cloning arises from the method used to remove the nuclei. In the most recent work, the nuclei were not mechanically removed but only functionally incapacitated by massive doses of X-irradiation. No attempt was made to confine exposure to X-irradiation to the nucleus. Such irradiation, if applied to human cells, may not only incapacitate the nucleus but also cause lethal damage in the rest of the cell.

It must be stressed that these efforts at cloning have been made in the interest of basic research on the process of development. The experiments have not been performed in an effort to provide a means of artificial human reproduction. In fact, R.W. Briggs, one primary researcher in this area, is opposed to any attempt to perform cloning on human material. From conversations with him, I believe that he would oppose such work even if it were approached as completely basic research with no possibility of application. Others take less conservative positions, and some actually advocate the development and application of such technology.

**Regulation of Technology Applications: How, By Whom and When?**

In considering the application of genetic technology, the simplest question to answer about regulation is that of when. The answer is now. Some machinery already exists. Some federally-funded research involving human subjects must be approved by an appropriate committee,"
and any human subject in such research must grant permission to perform experiments upon him.\textsuperscript{55} However, other machinery must be developed to deal with the more complicated and delicate issues. We are not ready, socially or legally, for embryo transplantation. We are not ready for cloning. The problems inherent in the former must be dealt with quickly, although I suspect we have more time with respect to the latter. For effective regulation of all genetic technologies, the law must act before the fact to prevent a problem, rather than after the fact to eliminate one. This may be difficult but it will be necessary.

Genetic counselling should be available on a voluntary basis. This should include pedigree analysis and appropriate screening of people suspected of carrying a genetic defect in the heterozygous state. Since this would be, in effect, voluntary preventative medical care, it should pose no legal problem. The experience in Hartford demonstrates that such screening can create social problems.\textsuperscript{56} I think this indicates that genetic counselling and screening should be accompanied by careful education which I believe can be accomplished. Everyone must at least be made aware of the basic principles of genetics and the randomness involved in the occurrence of genetic diseases.\textsuperscript{57} Anyone who can understand the randomness of a tossed coin landing as a head or tail should be able to understand simple genetics. Everyone must be made to understand that no one is to blame when an individual has such a disease.

Research must continue in the detection of carriers of genetic disorders and in the prenatal detection of homozygosity in a fetus. The recent ruling of the Supreme Court concerning abortion\textsuperscript{58} makes application of this technology simple. If a genetic disease is detected prenatally, the reproductive partners should receive immediate counselling. If the fetus would develop into a defective child, the parents should be advised to consider an abortion. I do not think defective in this sense is at all difficult to define. With sickle cell anemia, thalassemia major, Tay Sachs or any of a long list of very grave diseases, survival is limited and therefore the fetus is defective. In contrast, a disease such as diabetes causes abnormal symptoms, but these can be controlled easily and cheaply. Of course, abortion cannot be required, but the option must be made available. I assume that parents concerned enough to seek initial counselling and prenatal diagnosis would be even more concerned about the con-

\textsuperscript{55} Id. at 1, 7, 16.
\textsuperscript{56} See note 27 supra & text accompanying.
\textsuperscript{57} See the section SOME BASIC GENETICS supra.
\textsuperscript{58} Roe v. Wade, 93 S. Ct. 705 (1973).
sequences of giving birth to a genetically defective child. I believe in the availability of abortion for the sake of the parents, not for the sake of the fetus. As I read the recent ruling on abortion,\textsuperscript{60} the fetus before viability is essentially denied any legal rights. The primary, if not the only, concern is the mother. I know there are many who view abortion as murder, and all I can say is that I disagree. Nature is quite kind to us in that it very efficiently aborts many fetuses with genetic defects. In some studies, as many as 49.5 per cent of spontaneously-aborted fetuses had more or less than 46 chromosomes,\textsuperscript{60} a gross and easily detected biological mistake. Further, if abortion can now be performed legally and safely, a person who wishes to have an abortion performed has as much right to have it done as one who is opposed to abortion has to permit the pregnancy to go to term. That, as I view the Supreme Court ruling, is a very personal decision.

Regulation of \textit{in vitro} fertilization and embryo transplantation should not be particularly difficult. One hears that application of this technology will be fraught with danger. I think it really involves legal and ethical considerations which are little more complicated than those associated with artificial insemination. Sufficient experimentation must be done with animal systems to guarantee that these techniques themselves do not damage the fetus.\textsuperscript{61}

\textit{In vitro} fertilization and/or embryo transplantation should be performed only by qualified personnel, and the rights and responsibilities of all parties involved should be guaranteed \textit{before} any such action is taken. Specifically, if such reproduction is undertaken, the potential liabilities of the physicians performing the procedures must be predetermined as well as the rights of parent and child. My own view is that such reproductive technology can be justified within the context of basic research, but it hardly seems necessary or even appropriate to make extensive use of it in an applied sense.

If the technology of \textit{in vitro} fertilization and embryo transplantation is applied, it must be recognized by all involved that it is experimental and that mistakes can be made. Accordingly, when this experimental technology is used by a physician at the request of his patient, the physician must be protected and not held liable for damages under any circumstances. Biologically, it would be almost impossible to prove that the actions of the physician caused any damage. No physician should apply

\textsuperscript{59} Id.
\textsuperscript{61} No fetal damage was found with mice, Edwards, \textit{supra} note 40 & text accompanying, but it would be useful to have similar studies performed on organisms more closely related to man.
this technology against the wishes of any patient involved.

The rights and responsibilities of the gamete donors can be defined quite easily. When the donors comprise a natural reproductive pair, the fetus would be implanted in the uterus of the biological mother and the gametic parents would assume responsibility for the child produced. This situation is not essentially different from ordinary biological parenthood. If in vitro fertilization and embryo implantation is employed using sperm from a donor, regulation should be identical to that employed in artificial insemination. In fact, there seems to be little reason to use any technology beyond artificial insemination except in those rare cases in which a reproductive pair is simultaneously victimized by male sterility and functional female sterility from a Fallopian tube defect.

Regulation becomes more difficult when gametes are isolated from two persons, and the embryo is implanted in the uterus of a third. Several situations come to mind. If a reproductive pair are both carriers of a genetic disorder and do not wish to take the chance of producing a defective child, the simplest solution is artificial insemination. A heterozygous mother inseminated with sperm from a donor who is homozygous for the dominant allele would bear either a homozygous dominant or a heterozygous child. It is not beyond imagination, however, that this particular couple would be sufficiently concerned that they would not wish to produce even a heterozygous child. Gametes might then be derived from two noncarriers and used to produce an embryo, genetically unrelated to the heterozygous couple, which could then be implanted in the heterozygous female. Again, all rights and responsibilities must be determined before any such action is taken. The matter of custody and social and monetary responsibility for a child produced by such technology must be precisely defined. It must be impossible for gamete donors to decide they want the child if it is normal, and likewise it must be impossible for the recipients of the embryo to decide that they do not want the child if it is defective.

A further issue which is not easily resolved is that of fiscal responsibility for a defective child. Clearly I believe that the physician should not be responsible. Since the procedure would be entered into voluntarily, the persons assuming legal responsibility for the child should be held fiscally responsible. This essentially imposes a means test since many people might not be able to afford necessary medical treatment, but I see no reason why government at any level should be asked or required

to pay for such treatment procedure. It is not necessary to use such technology at great cost to produce more people when there already are so many in the world, particularly when many of these people are children available for adoption.

In other circumstances, \textit{in vitro} fertilization might be done using sperm and an egg from a pair who wish to have a child with implantation of the embryo into the uterus of a different female. This technique might be used where the female member of the pair does not wish to or is physically incapable of carrying a child.\textsuperscript{64} Such application of this technology could be regulated as proposed above.

The final aspect of genetic engineering to be considered is nuclear transplantation and cloning. This has received much attention in the popular press since it almost invariably either excites or frightens people. Articles on cloning sell magazines, but many of the articles I have read are misleading. They seem to imply that cloning either is possible today or will be in a very short time. They tend to point out potential social and legal consequences of cloning but disregard or misrepresent biological fact. Cloning is still technically difficult even in those organisms where it is possible, and it is not now possible in human beings.\textsuperscript{65}

The possibility of cloning human material leads one to consider the balance of the potential problems and dangers that such technology might generate versus its potential benefits. I acknowledge that I have real fears concerning the production of cloned human beings, and I also believe the potential benefits are overestimated. Cloning does produce an animal which is genetically identical to the nuclear donor. However, the genotype of an organism does not completely determine the phenotype. The phenotype is determined instead as the result of an interaction between the genotype and the environment.\textsuperscript{66} The same genotype in different societies will produce different phenotypes as the result of differing value systems, differing physical environments and differing historical periods.\textsuperscript{67}

\textsuperscript{63} A commonly proposed example is the professional woman.

\textsuperscript{64} Physical incapacity to carry a child to term may be caused by a number of different factors. One such factor is Rh incompatibility.

\textsuperscript{65} See notes 46-48 supra & text accompanying.

\textsuperscript{66} Phenotypic differences between identical twins, which are discussed in all textbooks of human genetics, are an example of this phenomenon.

\textsuperscript{67} If it were decided that intelligence is a desirable human characteristic and that it would be desirable to generate more people of more intelligence, then it might be suggested that cloned copies of known intelligent people be made. There is currently much argument concerning the degree of genetic control over intelligence, but there is at least partial genetic control. Jensen, \textit{How Much Can We Boost IQ and Scholastic Achievement?}, 39 \textsc{Harv. Educ. Rev.} 1 (1969). However, if the cloned fetus, or any fetus, for that matter, is exposed to rubella during the first trimester of development, that genetically determined intelligence will not be expressed. Furthermore, this interaction between the genotype and environment continues throughout life. The
Thus, even if it were possible to produce human clones, the traits of the cloned individuals would not necessarily be the same as those of the nuclear donor. Moreover, it is not certain that agreement could be reached concerning what traits make it desirable to create a cloned copy of a person.

It may be that cloning should not be undertaken for moral, ethical, religious, legal or scientific reasons. If it is undertaken, and I suspect that it will be, rigid controls will be mandatory. The only valid use I see for such work is to accumulate basic knowledge about the development of a human being. It is my opinion that if a successful cloning is performed with human material, no embryo should be permitted to develop for any extended period of time. The period of three months during which abortions cannot be prohibited strikes me as a reasonable limit to the development of a cloned individual. Such a limitation avoids many of the legal, if not moral and religious, objections to cloning. I base this conclusion, as well as my reservations concerning any artificial reproductive technology, not on any moral, ethical, religious or legal considerations, but rather on the necessity of solving the greatest problem of genetic engineering of all—the size of the human population.

**The Role of Population Size**

Figures concerning the size of the Earth's human population are unreliable even at present. Those from the past are even less reliable. From most estimates, the human population of the entire Earth in 0 A.D. was about equal to the present population of the United States—around 200 million. The total population reached one billion only 142 years ago, in 1830. It was two billion in 1930 and three billion in 1960. It is now about 4.6 billion and increasing exponentially. It is a simple fact that the Earth is finite. To be convinced of this one need only look at a picture of earthrise from the moon. A finite Earth can support only a finite number of people. In this sense, an analogy between the human population and a bacterial population can be made.

Cultures of bacteria can be grown in two basic ways—batch and continuous culture. In batch culture, bacteria are inoculated into a container of limited size which has a limited amount of medium. Cell division begins and continues until some component of the environment is

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use to which intelligence is put can be profoundly affected by environmental and social influences. This is true whether an individual is produced by simple sexual reproduction, artificial insemination, *in vitro* fertilization, embryo transplantation, cloning, or any other technology. No matter how a society is structured and no matter how primitive or complex a society is, an individual will be taught certain values of that society. These will influence how he uses his intelligence.

Growth then ceases. In fact, death usually occurs on a massive scale. The rate of cell division in a bacterial culture can be increased by an enrichment of the medium, and the final number of bacteria can also be increased by such an enrichment. However, one cannot escape the fact that population growth ultimately ceases in batch culture. In continuous culture, cells are inoculated into a growth chamber which provides for the addition of fresh culture medium and the removal of old culture medium and cells. The rate of input of fresh medium can be adjusted so that the cells are diluted out at a rate which precisely matches the rate of cell division. In such a culture, the cell density is constant. The human population lives in a batch culture in a finite growth chamber. The size of the population is increasing because of an imbalance in the equation: births = deaths.

Whether this equation has ever been balanced in the history of man is doubtful. It is not balanced now. It can be balanced by increasing the number of deaths or by decreasing the number of births. The former seems to me not only absurd, but also ineffective. The estimated 500,000 people who were killed in the natural catastrophe that recently befell what is now Bangla Desh were replaced by new births within the country in only forty days. All of the dead of World War I were replaced in less than a year. A catastrophe, natural or man made, would have to be of colossal proportions to have a significant effect on the size of the human population. Furthermore, the catastrophe would have to be cyclical since the population could recover after a catastrophe. Population growth will continue because, as the result of a massive effort at death control and little effort at birth control, births exceed deaths.

The rate of population growth has increased because the nature of our medium, the environment, has changed. We are fed better and have better medical care than in the past. It is suggested that the Earth can support many times the present number of people as the result of improved technology and that agricultural geneticists will breed us better plants and animals. All of this is the equivalent of enriching the bacterial medium. The upper limit of the number of organisms is raised, but a limit will still be reached. It is folly to predict what factor will limit the size of the human population or how large that population will be when a limit is reached. But the limit will be reached if the number of births is not reduced.

Achieving an equilibrium between births and deaths is the single most necessary aspect of genetic engineering. Without establishment of such an equilibrium the population will reach a limit at some time in the

near future and touch off a natural catastrophe of unprecedented proportions. Death will occur on a massive scale. The human survivors, if any, will be forced to live in such a primitive state that reproduction by any artificial means will be impossible. If we do not pay immediate attention to the limitation of our own population, we will not be given the time or opportunity to worry about artificial reproduction. If we do not give immediate attention to voluntary control of reproductivity, we may find ourselves living in a society in which we are told whether or not we can reproduce.

CONCLUSION

I have tried to suggest my views concerning regulation of reproduction, natural or artificial. But it is a simple fact that if we do not control our reproductivity voluntarily, control over that and many other aspects of the freedoms which we now enjoy looms large. The size of the human population and the necessity of controlling that size dwarfs other aspects of genetic engineering. The single greatest glimmer of optimism that I see is that we can now effect that control. We should deal with the biggest and most soluble problem of genetic engineering first. If we do that, we may survive to solve the others.