Genetic Engineering

by Robert L. Sinsheimer

The possibilities of genetic engineering derive from the great discoveries made in molecular and cellular biology in the past two decades, building, of course, upon the previous century of scientific advance in biology and genetics and in particular upon the profound understanding of the nature of matter provided by physics and chemistry in the first half of this century. These advances have included the comprehension of DNA as the basic substance of heredity; some grasp of the means by which this substance is reproduced—precisely, or with change as in mutation—of the means by which this substance directs the activities of the cells and thus the organs and thus the organisms; an understanding in outline, at least, of the way in which the DNA genes direct the synthesis of the complex proteins—the hemoglobins and hormones and enzymes that do the work of the body; a beginning knowledge of the detailed architecture of these complex proteins that enables us to see how they carry out their intricate molecular tasks—and also how they have evolved to their present state of efficiency—and more.

These are truly great intellectual triumphs. One might have thought that such great discoveries would provoke joy and zest for more in the pride of understanding. But these are troubled times on every front—times of intense self-doubt which corrode confidence and cripple resolve, and hence perhaps it is not surprising that these major scientific advances have also provoked fear and suspicion and troubled indecision.

Thus we read in an article by George Steiner: "It is as if the biochemical and bio-genetic facts and potentialities we are beginning to elucidate were waiting in ambush for man. It may prove to be that the dilemmas and possibilities of action they will pose are outside morality and beyond the ordinary grasp of the human intellect."

Or Sir McFarlane Burnet, the noted immunologist, has written: "Man, that dominant mammal, evolved in a middle-sized world: his curiosity has led him into two universes which are totally irrelevant to his evolution from mammal to man. The first, which concerns both the cosmic universe of the astrophysicists and the infinitely small world of the fundamental physical particles, is the process by which elements evolved in stars. The second is the chemical basis of life, the coded nucleic acid polymers that we call DNA and RNA. There is a third forbidden universe still to be effectively explored, the nature of what we call thought or consciousness and its relation to brain structure and function. It also is not relevant to human evolution, and its partial understanding may present us with greater perils than have come from our intrusion into the other two."

Do we face an ambush—or an epic opportunity? A forbidden universe—or the long-sought land, the goal toward which evolution has been striving for five billion years—to be in its product, aware of its origin and its essence, and thus to rise above the chance that has brought us to this time?

These are most certainly profound questions. We have over the past few centuries achieved a very considerable mastery over our physical world, and many are less than pleased with the results. We can now foresee—through our new insight into the bases of life—a growing mastery over our biological world—and that includes us—and many are terrified at the prospect.

They are not without reason. Much of the despair of our times stems from the realization that at last, after all the toil and all the invention, all the savagery and all the genius, the enemy is "us." Our deepest problems are now "made by man."

Now I should point out that genetic engineering is not only applicable to men. However, I expect that it is not the prospect of the application of the new knowledge to the biological world in general that frightens thoughtful

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men. If we can clone prize cattle to improve our food supply; if through designed genetic change we can produce more nutritious crops which make more effective use of sun and water; if we could, for instance, greatly expand the range of plants with the capacity to serve as hosts for nitrogen-fixing bacteria; if we can engineer viruses or microbes to curb pests or to destroy cancer; these innovations might produce ecological concern but not dire doubt. It is the possible application of genetic engineering to man that generates the shock wave. For this possibility, remote as it may yet be, illuminates from a new direction all that is encompassed in the word "human." Even the possibility of genetic engineering makes us ponder our understanding of the nature of man and thereby challenges traditional concepts in every area of human activity.

And much of the alarm is that we scientists, with our clever new tools, could crudely disrupt much of our social order—imperfect as it may be—with scant regard for its replacement. It has happened.

Out of the vast range of possibilities, I would like to discuss a small set which are, however, those which I think are most likely to be the more immediately feasible. I would like to emphasize that very little of what I am about to discuss is feasible today, but I can imagine that some components might become so within, say, the next two decades.

I want to discuss specifically, first, the detection of genetic defect and the related subjects of genetic counseling, amniocentesis, and the prospects for gene therapy. I would also consider the status of in vitro fertilization and the often-cited "test tube babies." Both these technologies also generate the possibilities of sex selection. A further development concerns the possibility of vegetative reproduction, or cloning, of human beings. And lastly we might briefly consider the issues posed by the ultimate possibility of a positive eugenics.

One consequence of our deepened understanding of inheritance and of the increased prominence accorded to this subject has been the surprised recognition that a very considerable number of our human ailments have genetic origins. This set of diseases has become particularly important as our ability to cope with the ailments of external origin—microbial disease and such—has increased. Over 2,000 different human disorders are now recognized to be the consequence of genetic defects. It is estimated that 25 percent of the hospital beds in the United States are occupied by sufferers from genetic disease. Because genetic disease often takes its toll early in life, the number of life-years lost per year due to genetic disease is far higher than the life-years lost due to the more widely known diseases such as cancer or heart ailments which more usually strike later in life.

This somewhat belated recognition of the importance of genetic disease has given rise to new activities designed to cope with it—to the profession of genetic counseling as a means for the prevention of genetic disease and to a search for possible means of genetic therapy.

Genetic counseling is a new profession based upon our increasing understanding of the genetic origin of human disorders and our increasing ability to recognize the genetic or chromosomal bases for these disorders—either in a prospective parent or in the developing fetus. The techniques for the discovery and analysis of single gene defects that obey Mendelian rules are well established; in an increasing number of these the biochemical defect is known and can be assayed, even in heterozygotes. Of course, the known existence of the defective gene in the parent only conveys a certain statistical probability of the appearance of the disorder in the fetus. The detection of such a defect in the fetal cells derived from amniotic fluid is more certain and is now possible in certain disorders by means of the new technology of amniocentesis. The detection of genetic disorders in fetal cells is presently limited to about 15 to 20 diseases, but it is plausible to suggest that means may be developed to permit the detection of a much wider range. The detection of such a defect in a fetus then permits the option of abortion.

The most urgent field for further advance in genetic counseling concerns those conditions which while subject to evident genetic influence cannot be attributed to simple single gene defects. In my view the evidence for a major genetic component in such widespread disorders as schizophrenia, diabetes, certain forms of cancer, susceptibility to heart disease, even rate of aging (if that is properly a disease) is unarguable. But we know as yet too little about the associated biochemistry even to know what to look for in the fetus.

One important possibility for further empirical advance in this field lies in the potential for more detailed chromosomal analysis. It is only within the past two years with the recent development of specific staining methods that it is possible to recognize uniquely each of the 23 human chromosome pairs. There is now clear evidence of the existence of marked differentiations along individual chromosomes and therewith the existence of previously unknown variations among the human population. It is possible that such variations may be correlated with some of these genetically complex disorders. (Parenthetically, it is an ironic commentary that one of the first uses to be made of this remarkable discovery has been to resolve cases of disputed parenthood.)

Further, it is at least possible that the differentiation along the individual chromosomes may by appropriate techniques be carried to much finer levels than are revealed by the light microscope. The visualization of submicroscopic differentiations along human chromosomes, if such exist, is certainly within our reach and is most worthy of exploration.

Of course the implications of such possible advances for genetic counseling are scientifically evident—and ethically confounding. For what conditions will one counsel genetic restraint—or abortion?

The genetic counselor already faces cruel and complex decisions. Suppose, for instance, he ascertains that a fetus or a newborn child has XYY chromosomal composition. He knows that this condition is associated, statistically but by no means invariably, with an increased tendency toward antisocial behavior. Should he, or is he required, to inform the parents of this condition?

Or suppose he ascertains that an adult is the carrier of a translocation which would give a statistical chance of a defective child, and therefore suspects that other members of that family may likewise be carriers. Is it his responsibility to seek out and inform these relatives?

And if a fetus is discovered to have an invariably crippling condition, should the decision to abort or not be solely that of the parents? Or does society have a role to play, when we note in this regard that the abortion, if performed, is primarily for the parents' or society's benefit? To argue that it is for the child's benefit is tricky ground.

The possibility of gene therapy would, of course, markedly alter the fateful character of decisions such as these. This prospect—which we can foresee—of detailed genetic premonition has many philosophic implications, but practically, I think, it is very likely that we will for some generations to come be faced with a situation in which we have increasing knowledge of individual genetic predestination, with limited means and probably limited will to eradicate the less adequate genes from the population—and therefore with a rapidly increasing demand for some techniques of individual genetic therapy.

Varied approaches to this end can be envisioned dependent upon the particular condition and the stage in life at which therapy can or must be applied. If we consider a single gene defect, the most evident therapy would be to supply a valid copy of the defective gene, incrementally. That is, if we consider a disease such as galactosemia or phenylketonuria or sickle cell anemia in which the individual lacks a good copy of a gene known to provide a specific function, the simplest procedure might be to provide that individual with a good copy of that gene by addition—by adding it to his genetic complement.

How might we do this? Various possibilities can be imagined, but I would like to mention only one which I think may be the most likely—through the use of what might be termed beneficial viruses. We think of viruses in general as rather destructive, and most are. They invade a cell, release their nucleic acid, reproduce, kill the cell, make more virus, and move on to the next victim.

But there is another class of viruses which enters into a more symbiotic relationship with the host cell. Such viruses invade the cell and release their DNA, but this DNA now, instead of reproducing, integrates with the host DNA. It is reproduced each time the host DNA is reproduced, so all the descendants of the original cell contain a copy of the viral DNA. Some of the genes of this DNA can be expressed while it is in this integrated state—so in effect a small set of new genes has been added to the complement of host cell DNA for an indefinite time.

Suppose now that one of the genes this virus brought in was the gene that was defective in a person suffering from galactosemia. If this gene were expressed, were functional, it could substitute for the defective gene of that individual.

We can already do just this trick in bacteria, and while we do not know just how to do it in humans, I think we are not that far from the possibility. While there are many unknowns as yet, and while much preliminary and precautionary work must be done—we, for instance, would certainly not want to run any risk of inducing a cancer while attempting the genetic therapy—I think the potential of this approach is obvious.

Of course, such a therapy will not suffice for all instances. It could not compensate for an extra chromosome, nor could it alleviate a disease in which serious lesions had already been introduced prior to birth, but it could be a powerful aid for many serious defects.

A partial consequence of the explicit realization of our genetic constraints and inequalities may be an increased impetus toward a more active or more eugenic attitude toward our collective biological inheritance. The successful achievement of in vitro fertilization of selected human eggs by selected human sperm, followed by uterine implantation and development, would be a major step toward such a technology. It should be noted that this has already been accomplished in other mammals such as mice; that is, it is now possible in mice with better than a 25 percent success rate to extract an ovum, fertilize it in vitro with sperm activated in vitro, allow the fertilized egg to develop to the blastocyst stage in vitro, implant the blastocyst in the uterus of a prepared mouse, and have a healthy delivery a few weeks later.

Preliminary experiments, directly analogous, are being performed with human ova and sperm.

Obviously, once the blastocyst is available, it need not be reimplanted in the original mother and the possibility of foster motherhood, "of wombs for rent," becomes quite real.

Such a technology, of course, affords the *possibility* of the selection of eggs and sperm from donors chosen for whatever eugenic objectives one might advocate. Indeed, banks of frozen sperm are already being established: The donor might even be some distinguished person long deceased.

In this day of Women's Lib, banks of frozen ova cannot be far behind.

Unless the success rate can be raised to 100 percent, one would have to face here the painful problem of "rejects." Many would, of course, simply fail to develop but a few might succeed, albeit with serious abnormality.

Since the sex of the blastocyst can be readily determined, this technology would permit pre-selection of the sex of the unborn child. Indeed, one should point out that if sex is acceptable as a criterion for abortion, amniocentesis already provides the same option. It is conceivable that other methods may be developed which might, for instance, permit the physical separation of X-chromosome-bearing sperm from those bearing Y chromosomes.

In any event, the possibility of sex selection would remove this choice from the realm of chance—in which it has lain for so long—into the arena of human decision. How might we cope with this new option? How would we arrange for equal numbers of men and women? Or would we want this distribution? More subtle questions arise: Surveys suggest that most families would choose to have their first child a boy, their second a girl. There are well-recognized psychological consequences of being the first child in a family, and these are very different for the two sexes. What might be the social consequences if there were no women who have been the oldest child or no men who have been the youngest child? If all women had an older brother and realized they were, in effect, a second choice?

The prospect of true "test tube babies," infants carried through fetal development in artificial uteri, is still remote in terms of present techniques—although its ultimate achievement if desired would seem entirely feasible.

A technology that appears much closer to hand is that of vegetative human reproduction or cloning. Cloning in principle removes the element of chance from the game of heredity. It replaces the genetic lottery with selection—based however, it must be remembered, upon one initial phenotype. The technology of cloning is derived from the concept that the nuclei of all cells of an organism contain its entire genome. Different portions of the genome are used in the cells of different tissues. This being so, it should in principle be possible to reproduce the entire organism manyfold by use of the genetic information replicated manyfold in its many cellular nuclei.

Such cloning has in fact been accomplished by nuclear transplantation in amphibia. Nuclei extracted from cells of young amphibia can be transplanted into previously enucleated eggs of the same species. Such eggs then develop with a small but real percentage of success into mature amphibia. Obviously the process can be performed with a considerable number of nuclei and eggs to produce a clone of genetically identical individuals, and it can be carried on through successive generations.

Cloning by nuclear transplantation has not yet been accomplished in man. But as far as is known only technical problems intervene. Could a nucleus be successfully transferred into an activated egg cell, the remaining steps are virtually in hand, as we saw in the discussion of in vitro fertilization.

Cloning would in principle permit the preservation and perpetuation of the finest genotypes that arise in our species—just as the invention of writing has enabled us to preserve the fruits of their life's work.

But man is certainly not an amphibian nor even a mouse. The relation of phenotype—the basis of selection—to genotype, which is selected, may be much less direct. I think there are profound questions to be asked before one can advocate this seemingly attractive shortcut to human genetic improvement. The first cloned man, the new Adam (or Eve), would be an orphan in a new and potentially poignant sense. He would be truly a child of the race, selected and produced by its collective wisdom. But how will he fit into our on-going society? How will he be received by his genetic relations—by his fellow clonees? The special psychological problems of twins have been extensively studied.

Assuming the phenotype reproduced as hoped, how would this Adam be received by his professional colleagues—as a superior, but a fellow, or as an alien to be outcast?

And how would he react to his special status in the world? Would he accept and enjoy it, or would he be likely to rebel against his predestination?

I hope these questions will be given serious thought before cloning—which may well be soon upon us—is attempted in a casual manner. It may well be that some of these matters can only be resolved by the experiment, but if so I hope such experimentation can be confined at first to a very small scale.

The larger possibilities for basic genetic change of our species beyond anything now known are fine for speculation, but certainly beyond our present capabilities. However, this does not mean that I think such possibilities will never be feasible. On the contrary, I am convinced they will, as we acquire new knowledge and understanding.

And this will give rise to grave questions and grave dangers. For what purposes should we alter our genes and to whom should we give such powers?

Many are opposed even to discussion of this subject. They argue, not implausibly, that we lack the intellect and wisdom adequate to assume such responsibility.

They question our intellectual capacity to foresee the probable results and if we could, they question our moral ability to define and choose the better.

As implied by McFarlane Burnet this point of view would question whether anything in the evolutionary history of our species had prepared us for this God-like role.

In one sense the only candid answer must be negative. It is in my view a miracle that the neuronal circuitry developed to cope with predators and permit adaptation to climatic shifts should also be able to comprehend the universe, to unravel the secrets of life, and its own origin.

But here we are—at this juncture in *our* evolution. We have really only two choices: to proceed with all the wisdom we can develop, or to stagnate in fear and in doubt. There is a consequence to either choice.

Now it can be argued, and indeed demonstrated, that given the apparently wide diversity of the human gene pool we have not begun to exhaust the possible favorable combinations in human inheritance. And it is also undeniably true that we should foster and preserve human diversity. It is the interaction of different human talents and points of view that most stimulates human progress.

But nevertheless from an evolutionary point of view it seems certain that there are limits to human capability, both physical, which most will concede, and intellectual.

I might suggest as one starting point that the facts of genetics and ordinary observation compel us to recognize the large element of predestination in our lives. Yet our internal reflections, our very quandaries, inform us that we as men are not wholly pre-programmed. We are confined within the finite sphere of our vision—yet we know perplexity and choice.

To me this element of reflection and self-reflection and choice is the core of humanity, and the object of any genetic engineering should be to enlarge our capacity for choice and to enhance our perception of consequence—to enlarge the sphere of our vision and to sharpen our tools for decision—and always to remember our finitude and thus our need for self-doubt and compassion.

More specifically, we might ask what in an evolutionary sense are the distinctive characteristics of the human species which—as we seize our destiny—we may wish to enhance? I would suggest a few, with no conceit that this is a complete list but rather with the intent to commence an inquiry:

1. Our self-awareness
2. Our perception of past, present, and future
3. Our capacities for hope, faith, charity, and love
4. Our enlarged ability to communicate and thereby to create a collective consciousness
5. Our ability to achieve a rational understanding of nature
6. Our drive to reduce the role of fate in human affairs
7. Our vision of man as unfinished

This is clearly a complex of characteristics; it is incomplete—and worse, for as of now we simply do not know to what extent these features of man are inherently coupled one to another, or maybe intrinsically hierarchical. I would hope that we might begin to explore these questions.

At the end of this discussion of issues sometimes sweeping and remote, sometimes immediate and anguished, we find we cannot escape the need to make the most crucial value judgments. Man *is* a social animal—the product of his culture as well as his genes. Inevitably there must be a progressive, developmental interaction between our social and our biological evolution. For what kind of a society shall we select genetic characteristics? To what kind of a society might the simple act of gene selection lead? Are some matters best left forever to the winds of chance? Or is that a failure of nerve and a denial of the human experience? Is it somehow inhuman to design a man?

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