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TOMORROW—OR THE DAY AFTER[1]

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Among the major problems confronting mankind today, three have reached, or are approaching the crisis level. These include *first*, a flagrant destruction of our environment; *second*, our reproductive success and decreased death rate, which have led to an unprecedented population explosion; and *third*, a deterioration of the human gene pool. Both ecology and the population explosion are receiving much attention these days, particularly since the political benefits of the former have recently been discovered. But the prospect of human genetic modification, either to decrease the frequencies of disadvantageous or lethal genes, or to modify the human genotype in certain preselected directions, has received little attention outside professional journals. Sober scientific thought concurs in the conclusion that control of human evolution is, indeed, a prospect for "tomorrow or the day after."

Our bank of genetic material is undergoing a slow but inexorable decline in quality. Several dysgenic influences contribute heavily to this qualitative dilution. Every successful technique which lengthens the life span of persons with inherited defects increases the likelihood that such individuals will reproduce and pass on their defective genes. Selection and survival of the less fit slowly but relentlessly increase the frequencies of these genes and the probability that they will occur in future generations. Moreover, the nearly continuous warfare in which man chooses to engage tends to siphon off the physically fittest and, often, the intellectually well endowed.

About three to four percent of all births carry some detectable, genetically based defect. Many of the bearers of these defect-producing genes die, some very early, others a little later, and a great many can look ahead only to a life of greater or lesser misery if, indeed, their deficiencies are not such as to impair their mental processes. An additional but unknown number of fetuses, homozygous for recessive lethal genes, abort spontaneously. Quite aside from considerations of birth control and death control, those who *are* born ought to have a chance for life free from this type of defect. On the other hand, they should not serve as additional sources of input for deleterious genes.

Three avenues of approach are available in meeting this kind of problem: (1) *directed recombination*, involving selection of those genes which will be permitted to perpetuate themselves; (2) *overriding the expression* of defect-producing genes without trying to control their frequencies; and (3) modifying or even replacing the defective genes themselves—that is, *genetic surgery*. These three approaches really translate themselves into the twin questions, "Can man control his own evolution?" and "If so, should he?" The first of these two questions lies in the province of the scientist, whereas the second, raising, as it does, profound moral,

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legal, and ethical considerations, will shortly concern all rational, thinking persons. I want to explore these matters briefly, raising questions and considering related problems. We shall not come to many final answers here; rather, we shall have to await the intelligent judgment of those who today are our students.

In some ways, gene selection, or directed recombination, is mechanically the easiest, though not necessarily the most satisfactory, solution to the problem of quality control in the human gene pool. It requires no sophisticated equipment, no techniques which have not been available, even practiced in other species, for years. Basically, it involves only the selection of parental stocks, those whose genes will be transmitted to future generations. The oldest technique would merely restrict child-bearing to those best fitted to perpetuate the species. But this raises significant problems. What are the standards? Who makes the decisions? Racially pernicious, politically unsound, such a solution is at best impractical, at worst dangerous.

Heterozygous "carriers" of defect-producing genes can now be identified by relatively simple tests in such varied inherited metabolic diseases as sickle-cell trait, cystic fibrosis, and galactosemia. Could we not limit or prevent reproduction by such persons? The problem of how that control might be accomplished becomes a very personal one when we remember that each of us carries at least one, and probably several, such lethal, semi-lethal, or disabling genes. Should control be exercised through advice and counseling? On a distressingly small scale we are doing this now. Should it be by governmental restraint, by legislation, with penalties for breaking the law, or even by compulsory sterilization? Once again, the question of who should make these judgments is an exceedingly difficult one. But, viewed coldly and impersonally, this approach does offer the advantage of being possible now in many instances, for it requires little more in the way of precise genetic knowledge than we already have.

If the concept of selective parenthood seems repugnant or impractical or dangerous, there is the additional problem of whether to allow fetuses that will express defective genes or which have been damaged by such drugs as thalidomide or LSD to come to term. To permit them to do so is regarded by some as the deepest kind of cruelty, both to the new person and to his family. By others, *not* to do so is classed as murder. The philosophy underlying selective, legalized abortion may well need reexamination. Both Colorado and Hawaii have recently taken significant forward steps in this regard, and an even more liberal reform has just been passed by the New York legislature.

On the other hand, still another avenue of directed recombination is, even now, open. Before long it may become much more practical as our knowledge of the human genotype and linkage groups increases. Rather than select certain *persons* who shall or shall not become parents, or which *embryos* will be allowed to mature, we may select the *reproductive cells* themselves. To a degree this is practiced now. Artificial insemination, so long applied with rather successful results in animal breeding, is currently used to a much more limited extent with mankind. But all too often no account is taken of the genetic constitution of the prospective mother and little more of the sperm donor. Ordinarily the goal is merely the *fact* of child production in families where it would otherwise not be possible and, incidentally, to produce children who could be mistaken for those of the non-biological father.

The late Herman Muller (1965) proposed setting up sperm and egg banks, since sex cells can be kept alive and functional for considerable periods by freezing. Muller proposed such banks, with the most desirable male and female subjects serving as donors. By whatever standards that might be set up, the best sources could continue so to serve for a considerable period after their deaths and, with suitable precautions, even after a nuclear war. The question of determining genetic desirability here is of course no easier than in other systems of restrictive parenthood. But Muller expressed hope in these words: "With the coming of a

better understanding of genetics and evolution, the individual's fixation on the attempted perpetuation of just *his* particular genes will be bound to fade. It will be superseded by a more rational view . . . he will condemn as childish conceit the notion that there is any reason for his unessential peculiarities, idiosyncrasies and foibles to be expressed generation after generation." Society has not reached the stage of objectivity envisioned by Muller, of course, and gamete banks still entail an element of chance in recombination of disadvantageous genes, though the overall probability might be lower than in a system of random mating.

The techniques are, again, relatively simple. Use of sperm requires no more elaborate methods than those currently used in the practice of artificial insemination. Implantation of selected eggs, fertilized or unfertilized, is already a fact in laboratory animals and involves little that is new for adaptation to humans. Early this year a team of British doctors disclosed that an egg, already fertilized *in vitro* by sperm from the husband, is to be implanted in the womb of a woman who cannot conceive because of an obstruction in her fallopian tubes. It is entirely possible that the first test-tube conceived child will be born this year. Certainly there are difficulties ahead, and many presently unanticipated problems will doubtless arise. But work in this direction *is* going on, and success *will* come.

Once the process of implantation is perfected, the prospects are virtually limitless. The prominent British embryologist Cohen suggests the possibility of a system of volunteer "host" mothers who would bear other people's children for a fee where, perhaps, it may be physically unwise for a woman to undertake the risks and rigors of pregnancy, or even in case she simply does not wish to interrupt a career. Or, an infertile woman could bear children who are the product of her husband's sperm and ova from an unknown donor; such a fertilized egg might simply then be implanted in her body. Of course, the matter is more complicated than I appear to suggest, but surely it will be feasible in the relatively near future.

Some writers, only partly with tongue in cheek, have compared human germinal choice to selection of a packet of desirable flower seeds in the supermarket. The container could carry a brief statement of the most probable traits, from intelligence to physical perfection and even sex; selection could be made as simply as deciding on the kind of plants to grow. From the psychological standpoint, there is considerable doubt that man is ready for this, and our genetic knowledge of the human species is not yet up to our understanding of marigolds and petunias.

When it is, perhaps rather than implant an egg in a human female, we could not only select sperm and egg and bring about fertilization *in vitro*, but even raise the embryo to term in a glass womb. In fact, Petrucci in Italy is said to have raised human embryos in this way for as long as two months, and then deliberately terminated the experiment. The moral question "Is it murder"? is reported to have deeply disturbed him as a Catholic. Others have worked and are working along these lines and someday, somewhere, someone is going to be successful in producing such a person. Think of the cognate problems: who is he? who is or are his parents? what are his legal rights? Will we mass-produce a new race of slaves? One day these questions, and more, are going to have to be answered.

Further afield, but interesting speculatively, is the possibility of vegetative multiplication. It has long been possible to maintain cultures of human cells; will it eventually be possible to induce differentiation and thereby create unlimited numbers of identical individuals to certain specific genetic designs? Already we can do this with lower forms of life, and some scientists feel it is more a question of "when" than "if." Science fiction? Today, yes; but tomorrow? or the day after?

As another approach, consider the modification of the expression of the genes that one has, or even of replacing certain genes with their alternative alleles. Diabetes, for example, is a genetic disorder which affects several million persons

in this country, many of whom are kept alive only by injection of the hormone, insulin. This is one of the simpler proteins synthesized by the human body and its structure is well known, consisting of two polypeptide chains, one of 21 amino acid residues, the other of 30. It is formed only in certain cells of the pancreas from its precursor protein, proinsulin. Proinsulin is manufactured in the usual biological way, in which the appropriate base pair sequences of DNA are transcribed into mRNA which, in the cytoplasm, together with the necessary amino acids, ribosomes, enzymes, tRNA, and so forth, translates these sequences into protein. Using Benzer's terminology, only two DNA cistrons, of some 63 and 90 nucleotide pairs, respectively, are involved, representing altogether only about 0.05 micron of the total length of human DNA.

All somatic cells are believed to contain all the genetic information of the individual, yet only a very restricted group of cells synthesizes proinsulin. In other cells of the body, the proinsulin cistrons are "turned off," or repressed. Knowledge of the mechanism of gene repression in higher organisms is progressing rapidly, and one approach in treating diabetes may lie in learning how to derepress the proinsulin cistrons, either in the cells where it is normally produced or in other cells of the body. Once such activation has been achieved, there remains the problem of conversion of proinsulin to insulin and its release from the cells in which its synthesis is effected. By comparison, this may not be difficult and might, indeed, occur naturally. But such derepression in somatic cells, even for millions of diabetics, will have no effect in upgrading the human gene pool.

On the other hand, we may be dealing not with repressed genes but rather with cistrons whose deoxyribonucleotide sequence specifies a "wrong" series of amino acids. Even a single base-pair change—for example, a switch from an adenine-thymine pair to one of guanine-cytosine, or even from an adenine-thymine to a thymine-adenine pair, or a deletion or an insertion of one nucleotide pair, can code for an incorrect amino acid at given positions in the polypeptide chain and result in the formation of an aberrant or a non-functional protein. This is the sort of thing which spells the difference between normal hemoglobin A and hemoglobin S which is associated with sickle-cell disease. Could such defective cistrons be replaced by genetic surgery? In brief, the answer today for human beings is, "No, not yet." But it can be done in bacteria, though we cannot yet control very well which genes are replaced. One of the mechanisms by which this process occurs naturally in bacteria is transduction, a process involving transfer of DNA from one cell to another through the mediation of a bacterium-infecting virus, or phage.

In the infection of a bacterium by a virulent phage, the virus DNA is replicated in the bacterial cell, new protein shells of the virus are manufactured in the cytoplasm, and, after about half an hour, the bacterial cell bursts, releasing several hundred new virus particles ready to repeat the process. The vast majority of these contain DNA identical to that of the original infecting phage. But a very few contain a segment of bacterial DNA from the host cell, replacing a corresponding bit of viral DNA.

Some phages do not regularly produce this bursting and destruction of the bacterial cell. These are the temperate phages, one of which is known as lambda. Infection of a cell with lambda results in incorporation of some of the viral DNA into the bacterial cell's DNA. The bacterial cell survives and multiplies, some of its descendants containing DNA that includes sequences of nucleotides received from the virus.

The question here is whether this same kind of transfer of genetic material could be effected in the cells of higher organisms. There is evidence to suggest an affirmative answer. Aaronson and Todaro (1969) reported that DNA isolated from simian virus 40 can become established in human fibroblast cells *in vitro*

and appears to express itself in protein synthesis in such cells. SV40 is a small virus which produces tumors in appropriate animal hosts. Human cells in which SV40 DNA has been incorporated undergo certain characteristic changes, including loss of sensitivity to contact inhibition of cell division, and production of SV40-specific mRNA. Such human cells also produce a new protein, the so-called T-antigen, which persists in clonal cells. Aaronson and Todaro conclude their report with these words: "There is considerable evidence [to show] that SV40 DNA can become a permanent part of the host cell genome. Most of the SV40 DNA in transformed cells is associated with the chromosomes . . . However, if the viral DNA's ability to integrate into the human cell genome can be separated from its [tumor producing property], it may then be possible to use 'integrating' viral DNA to insert specific information into human cells." The important point here for our purposes is the incorporation and persistence of viral DNA in the human gene complement and its subsequent manifestation in specific new protein synthesis.

Two additional recent discoveries complete the groundwork for human genetic surgery. Rather than search for a convenient transducing virus carrying, say, a stretch of DNA for proinsulin production, it should be possible sooner or later to make it to order. In late 1967, Kornberg and his colleagues (Goulian, Kornberg, and Sinsheimer, 1967) reported the synthesis of biologically active DNA, of phase ΦX–174, some 6,000 deoxyribonucleotides in length. It is true that this virus's DNA is only single stranded and that to synthesize it these men used natural phage DNA as a primer. But the important point is that functional DNA had been manufactured experimentally for the first time.

Then just last November, Beckwith and his associates at Harvard (Shapiro, *et al.*, 1969) isolated and photographed a specific part of the lac operon, the segment of DNA responsible for the metabolism of lactose in the colon bacillus (*Escherichia coli*). They employed two transducing phages to obtain in pure form one cistron which specifies beta-galactosidase, the first enzyme in the system, together with the operator and promoter sites of the operon. These latter two are, in effect, genetic "switches," which direct the cistron to start or stop production of the specific mRNA which translates the genetic information of DNA into the polypeptide chains of the enzyme. The beta-galactosidase cistron consists of some 3,700 deoxyribonucleotide pairs, the operator and promoter sites together about 400. Hopefully, then, we will soon have the capability of isolating or synthesizing a nucleotide sequence coding for proinsulin and, perhaps, even of packaging it in a virus-like protein coat. Once the original synthesis or isolation has been performed, it is done for all time; following Kornberg's methods (Goulian *et al.*, 1967), it can then be copied accurately forever.

By the same techniques and processes, then, *any* faulty or undesirable gene could be changed, first in the somatic cells of individuals requiring such genetic surgery, and next in the reproductive cells, for there are two facets to the task here. It is one thing to modify the genetic material of the somatic cells, but to exercise a quality control over human evolution, such modification will, of course, also have to be made in the sex cells. We are, however, still left with the problem of defining desirability in the genome; that is, desirability from whose viewpoint? It seems to me that it is our compelling duty as scientists to continue vigorously to push back the veil of the unknown, and to seek out the truth, wherever it may lead. In that effort there must be no cessation. But it appears equally apparent that, as scientists, we have the inalienable duty to point out the consequences of the use or misuse of new discoveries. No scientist, I believe, should ever withhold new facts or new techniques because of fear of where their misuse might lead. But we should always be ready to alert the non-scientific community to potential dangers of misapplication.

If a few small cistrons can be synthesized, next will come the possibility of replicating the entire human DNA complement, literally making human beings

to order with almost any set of predetermined characteristics. Combine, if you will, this kind of genetic surgery or synthesis with the glass womb, and man will, indeed, then control his own evolution, shaping it to suit whatever the need, good or evil. And he *will* be able to do so, if not tomorrow, then surely the day after.

Truly, a new horizon in the history of man is just ahead. As Albert Rosenfeld (1969) has written in this context, "The time ahead is wild and unchartered." Wild and unchartered, yes; challenging to man's conscience, certainly; but assuredly exciting beyond our present capacity to comprehend.

REFERENCES CITED

Aaronson, S. A. and **G. J. Todaro.** 1969. Human Diploid Cell Transformation by DNA Extracted from the Tumor Virus SV40. Science 166: 390–391.

Goulian, M., A. Kornberg, and **R. L. Sinsheimer.** 1967. Enzymatic Synthesis of DNA, XXIV. Synthesis of Infectious Phage ΦX–174 DNA. Proc. Nat. Acad. Sci. (U.S.) 58(6): 2321–2328.

Muller, H. J. 1965. Means and Aims in Human Genetic Betterment. In T. M. Sonneborn (ed.), The Control of Human Heredity and Evolution. The Macmillan Co., New York. 127 p.

Rosenfeld, Albert. 1969. The Second Genesis. Prentice-Hall, Inc., Englewood Cliffs, N. J. 327 p.

Shapiro, J., L. Machattie, L. Eron, G. Ihler, K. Ippen, J. Beckwith. 1969. Isolation of Pure *lac* Operon DNA. Nature 224: 768–774.