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The Prospect of Designed Genetic Change

"It has now become a serious necessity to better the breed of the human race. The average citizen is too base for the everyday work of modern civilization. Civilized man has become possessed of vaster powers than in old times for good or ill but has made no corresponding advance in wits and goodness to enable him to direct his conduct rightly." This was written in 1894 by Sir Francis Galton. The concerns of the present are clearly not new.

It has long been apparent that you and I do not enter this world as unformed clay compliant to any mold; rather, we have in our beginnings some bent of mind, some shade of character. The origin of this structure—of the fiber in this clay—was for centuries mysterious. In earlier times men sought its trace in the conjunction of the stars or perhaps in the momentary combination of the elements at nativity. Today, instead, we know to look within. We seek not in the stars but in our genes for the herald of our fate.

Today there is much talk about the possibility of human genetic modification—of designed genetic change, specifically of mankind. A new eugenics has arisen, based upon the dramatic increase in our understanding of the biochemistry of heredity and our comprehension of the craft and means of evolution. I think this possibility, which we now glimpse only in fragmented outline, is potentially one of the most important concepts to arise in the history of mankind. I can think of none with greater long-range implications for the future of our species. Indeed this concept marks a turning point in the whole evolution of life. For the first time in all time a living creature understands its origin and can undertake to design its future. Even in the ancient myths man was constrained by his essence. He could not rise above his nature to chart his destiny. Today we can envision that chance—and its dark companion of awesome choice and responsibility.

It is all too easy, albeit useful, to let our imagination in these matters roam far beyond our technical base. It is easy, even for modest men given to cautious projection, because in truth all that seems needed is the technology and the resolution to transfer to man what we already know to be feasible in bacteria or carrot cells or frogs. It is easy because there are no known natural laws to repeal or contravene. None of the time warps or hyper-drives or teleportation of science fiction are needed to envision vegetative reproduction, organ regeneration, genetic therapy, or eugenic transformation of our species.

I would like, however, to consider a very specific and possible use of our newer knowledge, relating to a major biomedical problem. This application may well seem of small dimensions as compared to some of the more sweeping prospects, but I believe it will illuminate the state of our knowledge and our technology and will thereby reveal the shape of things to come.

I want to use the phrase "genetic change" in a broad sense, in the sense of altering some physiological or psychological process which at present we believe has been programmed into us through our inheritance. And I will assume that such change might be achieved either in a strictly genetic mode through a change in our inherited characteristics, or in a somatic (non-inheritable) mode—possibly through a change in the time or place or degree of action of our inherited genetic components, or

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chairman of the division of biology, discusses the possibility of human genetic modification—

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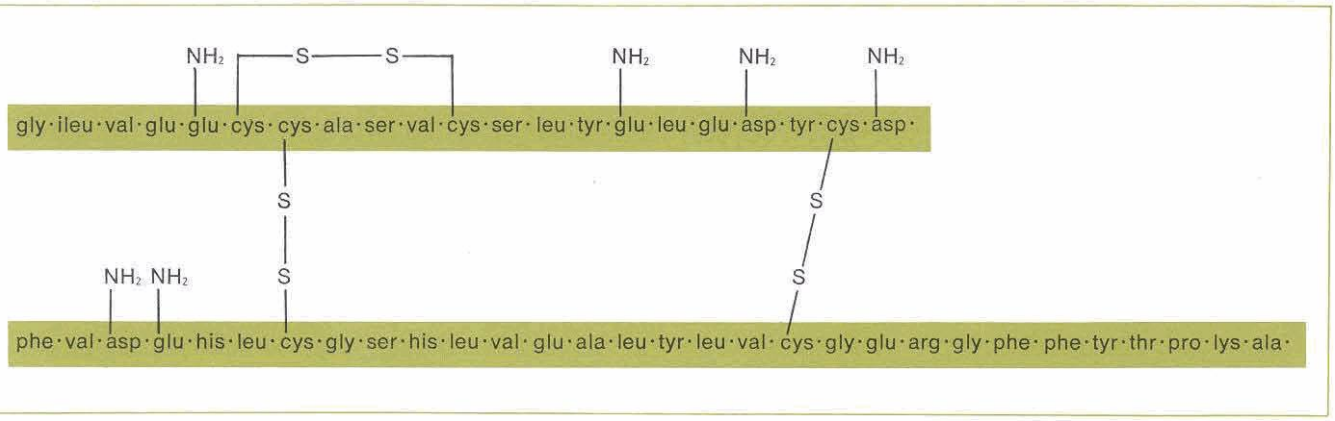
possibly through the somatic addition of genetic components. Obviously changes of the former—the truly genetic type—have the greater ultimate potential; for the very nature of the species seems potentially susceptible to change. Changes of the latter type—somatic genetic modifications—are more limited. Their scope and function are the more restricted, but they are also undoubtedly the more accessible possibilities which we will first achieve.

There are in the United States today some 4,000,000 clinical diabetics. Many of these people are kept alive only by repeated, frequent injections of the hormone insulin. It is believed that there are several million more cases with marginal symptoms. Without recurrent injections of insulin many of these people would perish. While it keeps them alive, the injection of insulin is not the full equivalent of a normal physiological function; diabetics are known to be more susceptible to disease, to heart and circulatory illnesses, and other physical limitations than non-diabetics.

I propose that genetic therapy offers the promise of a much more elegant, and indeed more satisfactory, physiological solution to this ailment. And there are various possible genetic approaches.

To begin we must understand the normal process of insulin formation. Insulin is a protein, composed of two polypeptide chains—one of 21 amino acids and one of 30—joined by two disulphide bonds. There is recent evidence that indicates strongly that the insulin molecule is initially formed as a single polypeptide chain, and an internal segment is subsequently excised by the action of a specific proteolytic enzyme.

The synthesis of this protein, the proinsulin, is accomplished in the usual manner: The hereditary instructions specifying the sequence of amino acids for insulin are encoded in a segment of the DNA

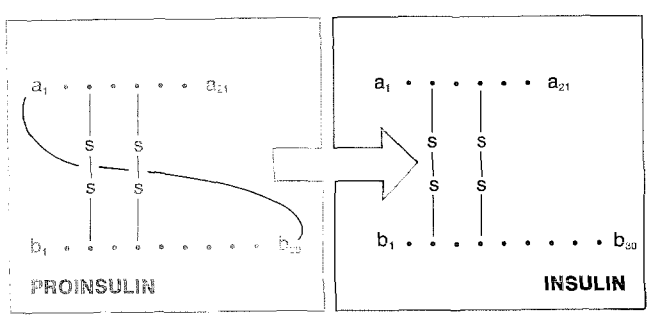


The chemical structure of human insulin consists of two polypeptide chains, one of 21 amino acids and the other of 30, which are joined by two disulphide bonds.

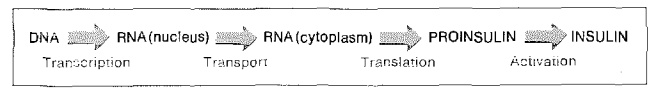
from the cell nucleus. The instructions are copied and transcribed into a messenger RNA molecule which then is transported out of the nucleus to the cytoplasm. There protein synthesis takes place upon the ribosomes. In this process the sequence of nucleotides in the RNA is translated into the corresponding amino acid sequence with the help of the transfer RNA molecules, the activating enzymes, the initiators, the coupling factors, and all the rest of a very complex machinery.

It is well known that this synthesis of insulin normally takes place only in the beta cells in the Islands of Langerhans in the human pancreas. In the diabetic these cells fail to produce an adequate amount of insulin. Now it is believed, and there is good reason for this belief from studies of lower animals, that the *full* DNA content of the genome is present in every somatic cell. And thus we believe that the genetic instructions specifying the sequence of proinsulin are present in all the cells of the body and not only the beta cells of the Islands of Langerhans. Evidently these instructions, though present in other cells, are not in use. Either they are not activated, or, as it is more fashionable to assume these days, they are repressed. Repression could take place at any of several levels.

A typical somatic cell is only called upon to use a small fraction of its genome. There is good evidence that in a liver or a muscle cell no more than 5 percent of the DNA is ever transcribed into RNA, so there is repression at the chromosomal level. Further, it is clear that perhaps half or more of that which *is* transcribed never reaches the cytoplasm to be translated. And even if the RNA reaches the cytoplasm, there is evidence for specific blocks at the translational level. There are clearly many opportunities for the restriction of expression of the inherited genetic instructions.



This schematic drawing of the conversion of proinsulin to insulin illustrates the recent evidence that the insulin molecule is formed as a single polypeptide chain and that an internal segment is subsequently excised by the action of a specific proteolytic enzyme.



Steps in the biosynthesis of insulin. Repression of insulin synthesis could take place at any of these stages.

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

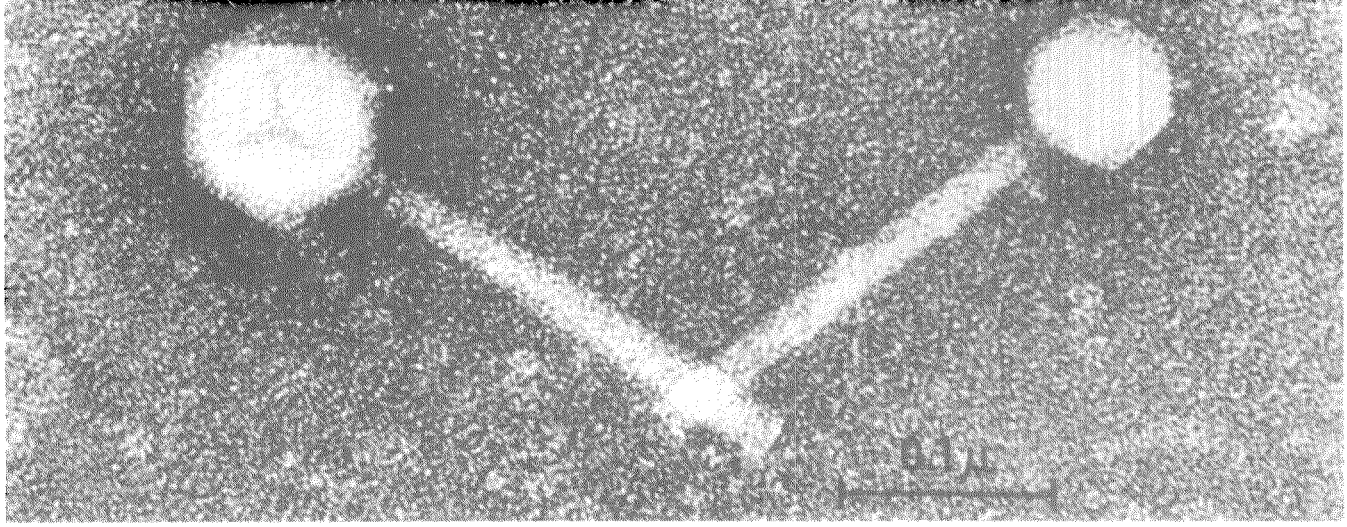
We do know that genes can be turned on by external influence. Hormones do this every day. For example, under the influence of cortisone, liver cells initiate the synthesis of a variety of enzymes including tryptophan pyrrolase and tyrosine-alpha-ketoglutarate transaminase.

In some instances the prior repression appears to be lifted hormonally at the chromosomal level of transcription, in others, at the translational level. We do not now know how we might do this for insulin, but we can see a clear model. And in fact just such an activation or derepression for insulin *must* have occurred through some chain of ontogenetic events during embryonic development to activate—to turn on—the appropriate genes in the beta cells of the Islands of Langerhans.

We should not oversimplify this problem. Obviously if we want a new group of cells to synthesize insulin, we must not only activate the gene for proinsulin but also arrange for its conversion to insulin and for its release from the cells. But, if we were fortunate, these functions might all come as a genetic package.

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

How might we add, in such a specific manner, to the genetic components of a cell? Our models come from studies with bacterial cells. In these organisms a variety of means exist to permit exchange and in so doing to provide small increments of genetic material. These include transformation, contact



Transduction (the transfer of genetic material from one cell to another) can be observed with the bacterial virus P 1. In this electron micrograph of P 1 virus the one-inch line (lower right) represents 1/10 of a micron.

transfer both chromosomal and episomal, and transduction both general and specific. Organelles for contact transfer are not known among mammalian cells, and transformation as such has not yet been convincingly demonstrated in mammalian cells. Therefore, the possible use of transduction as a means to genetic modification of cells of higher organisms should be specifically considered.

Transduction among bacteria involves the transfer of genetic material, DNA, from one cell to another through viral mediation. I would like to present two particular cases.

The first case is that of the bacterial virus P 1, which contains one molecule of DNA of about 60,000,000 in molecular weight. Upon infection of the cell by certain types of P 1, the cell is lysed (broken down) after half an hour to produce a few hundred progeny virus particles. Most of these will contain a DNA identical to that of the virus that initiated the infection. However, a little less than 1 percent of the particles will contain *instead* a piece of the DNA of the chromosome of the host bacterium, a piece also about 60,000,000 in molecular weight. Which piece of DNA—which particular 60,000,000 out of the 3 billion molecular weight of host DNA—is random. The particular virus will contain the piece carrying, say, genes D and E, while another carries a piece with the genes P and Q, etc.

By appropriate means these particles carrying host DNA, called transducing particles, can be separated from those carrying the normal viral DNA. When such transducing particles are added to susceptible bacteria, the DNA inside the virus particle is, in the usual way of bacterial viruses, injected into the cell. But *now* we have added to the cell not a destructive virus genome, but a piece of bacterial DNA which may well carry genetic markers not present in this particular host. This DNA may be transcribed at once to yield new protein.

For this piece of DNA to perpetuate itself, however, it must, in general, become incorporated *into* the host chromosome by a process of genetic recombination. Normal bacterial cells have the enzymatic machinery to do this, and, in the case of the transducing particles of phage P 1, there is about one chance in ten that the particular piece of DNA will be so incorporated and perpetuated.

In bacterial cells there are often small secondary chromosomes—episomes—usually containing 1 or 2 percent as much DNA as the principal chromosome. These are physically separate from the principal chromosome, but usually replicate in synchrony with it. It is possible for a P 1 phage to pick up and transfer an entire episome as well as a piece of bacterial chromosome.

A second case of transduction concerns the temperate (frequently non-lethal) bacteriophage lambda. Upon infection with the bacteriophage lambda, the result in an appreciable percentage of the cells (it can be the majority) is the physical incorporation of either the viral DNA or of one of its descendents into the chromosomes of the host. Following this, the *virus-like* tendencies of this DNA are suppressed. The cell survives and multiplies, and the incorporated viral DNA is replicated into each daughter cell along with the rest of the bacterial chromosome. Such a virus-carrying cell is said to be a lysogen.

An important feature is that the point of insertion for the lambda DNA into the host DNA is specific, and it is determined by the particular virus which in turn specifies an enzyme—an integrase—which

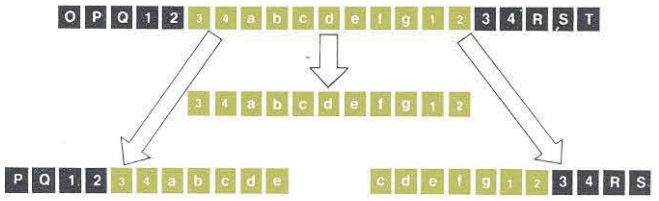
brings about its incorporation at that site. Related strains of lambda-type viruses are known which integrate into *other* chromosomal sites because they have different integrases.

It is possible, however, to induce an activation of this carried viral DNA in the lysogenic cells—to cause it to remember that it really is a virus, to cause it to break out of the bacterial chromosome, to begin to multiply, to produce progeny, and to lyse the cell, producing new virus particles.

Occasionally in such an activation, which is called induction, the piece of DNA which splits out of the chromosome is not strictly the viral genome but may incorporate a piece of the neighboring bacterial chromosome with its genetic material in lieu of a piece of the viral genome. Under certain circumstances viral development can proceed anyway. Such pieces of DNA, partially viral and partially host, can multiply and can be incorporated into virus particles. Particles with this mixed DNA can be isolated from the bulk of the progeny. If they are now added to susceptible cells, this DNA can still integrate into the host chromosome at the same locus but now adding along with the viral genes a specific piece of DNA from the former host—which may carry specific novel genetic traits into the new host.

In both of these cases, then—P1 and lambda—the net result is the introduction, via a particle normally indistinguishable from a virus, of new genetic material into the host cell. In the first instance the new factors added are random relative to the host genome. In the second, they are factors found at specific sites near the normal region of integration of the virus. The region varies in different viruses.

Could a similar transfer be accomplished with a virus in the cells of higher organisms? We have every reason to think that it does occur. Upon infection of mammalian cells with the simian virus 40, or with polyoma virus, or with some strains of adenovirus, in a fraction of such infected cells the viral DNA becomes established within the cell. Whether it is integrated into the chromosomal DNA or is an episome is not known. It is then perpetuated within the clone of cells descended from the original infected cell, as in a lysogenic bacterium. The information carried in the viral DNA is certainly expressed; cells carrying such DNA have altered properties; that messenger RNA derives from this viral DNA can be demonstrated; new protein antigens have been detected within such cells; and in special



In excision of a lambda DNA from the host chromosome, normal excision (center) yields one complete viral genome, while abnormal excision (left and right) yields mixed genomes, part viral and part host.

circumstances the entire genome of the virus can be recovered (and hence must have been present) from remote descendents of such altered cells.

Technically and literally the stage is set. If we could obtain a virus analogous to simian virus 40—able to persist within altered cells and carrying an expressible gene for proinsulin in lieu of a normal viral gene—we might indeed be able to provide a genetic alternative to the daily injection of insulin.

The problem then is, where are we to find this virus so propitiously carrying a gene to provide insulin? Such a virus might exist in nature, but I propose that we should quite literally, in time, be able to make it to order. We will have the ability in the not distant future to synthesize a polynucleotide chain capable of coding for insulin and for the other genes necessary to integrate the DNA into a chromosome, or to maintain it as an episome, or whatever. And we will then also be able to package this *de novo* DNA into an appropriate virus coat.

Is this pure fantasy? No, not really. The DNA of simian virus 40 consists of a chain of 5,000 nucleotides. The art of specific polynucleotide synthesis is young but thriving. It is now feasible to construct a specific sequence of 50 deoxyribonucleotides. A sequence of up to 100 seems close at hand, and a thousand or a few thousand is by no means inconceivable.

Furthermore, such a synthesis needs to be done only once. Once the DNA is available, nature provides the means to copy it with the highest fidelity.

Similarly, our understanding of the process of viral self-assembly is growing swiftly, and but a small step behind is the art of viral assembly *in vitro*. The technology needed for such a radically different approach to a major clinical problem is almost in reach.

Though the analogy is not perfect, in describing these prospects I feel strangely akin to the physicists who pointed out in the 1930's that the principles

required for the release of the energy locked in the atomic nucleus were understood. All that was needed was a practical breakthrough and the requisite technology. Here, too, the principles seem in hand. All that seems really needed is optimism, sustained effort, and support commensurate with the importance of the problem.

The larger and the deeper challenges—those concerned with the defined genetic improvement of man—perhaps fortunately are not yet in our grasp, but they are etched clear upon the horizon. We should begin to prepare now for their reality.

It is worthwhile to consider specifically wherein the potential of the new genetics exceeds that of the old. To implement the older eugenics of Galton and his successors would have required a massive social program carried out over many generations. Such a program could not have been initiated without the consent and cooperation of a major fraction of the population, and would have been continuously subject to social control. In contrast, the new eugenics could, at least in principle, be implemented on a quite individual basis, in one generation, and subject to no existing social restrictions.

The old eugenics would have required a continual selection for breeding of the fit, and a culling of the unfit. The new eugenics would permit in principle the conversion of all of the unfit to the highest genetic level.

The old eugenics was limited to a numerical enhancement of the best of our existing gene pool. The horizons of the new eugenics are in principle boundless—for we should have the potential to create new genes and new qualities yet undreamed. But of course the ethical dilemma remains. What are the best qualities, and who shall choose?

It is a new horizon in the history of man. Some may smile and may feel that this is but a new version of the old dream of the perfection of man. It is that, but it is something more. The old dreams of the cultural perfection of man were always sharply constrained by his inherent, inherited imperfections and limitations. Man is all too clearly an imperfect and flawed creature. Considering his evolution, it is hardly likely that he could be otherwise. To foster his better traits and to curb his worse by cultural means alone has always been, while clearly not impossible, in many instances most difficult. It has been an Archimedian attempt to move the world, but with short arm of a lever. We now glimpse another route—the chance to ease the internal strains and heal the internal flaws directly, to carry on and consciously perfect far beyond our present vision this remarkable product of two billion years of evolution.

I know there are those who find this concept and this prospect repugnant—who fear, with reason, that we may unleash forces beyond human scale and who recoil from this responsibility. I would suggest to them that they do not see our present situation whole. They are not among the losers in that chromosomal lottery that so firmly channels our human destinies. This response does not come from the 250,000 children born each year in this country with structural or functional defects, of which an estimated 80 percent involve a genetic component. And this figure counts only those with gross evident defects outside those ranges we choose to call natural. It does not include the 50,000,000 "normal" Americans with an IQ of less than 90.

We are among those who were favored in the chromosomal lottery, and, in the nature of things, it will be our very conscious choice whether as a species we will continue to accept the innumerable, individual tragedies inherent in the outcome of this mindless, age-old throw of dice, or instead will shoulder the responsibility for intelligent genetic intervention.

As we enlarge man's freedom, we diminish his constraints and that which he must accept as given. Equality of opportunity is a noble aim given the currently inescapable genetic diversity of man. But what does equality of opportunity mean to the child born with an IQ of 50?

The application of knowledge requires technology, but the impact of knowledge can precede its application. Knowledge brings understanding, and the consequences of understanding can overflow the mind into the heart. It may be that in the near future the most important consequence of our new knowledge of ourselves will be a new sense of the power and responsibility—of the pivotal role—of man in this universe. Copernicus and Darwin demoted man from his bright glory at the focal point of the universe to be merely the current head of the animal line on an insignificant planet. In the mirror of our newer knowledge we can begin to see that in truth we are far more than another ephemeral form in the chain of evolution. Rather we are an historic innovation. We can be the agent of transition to a wholly new path of evolution. This is a cosmic event.