Reprinted from *Man and his Future*, 1963, pp. 263-273.
(A Ciba Foundation volume edited by Gordon Wolstenholme.)
Published by J. & A. Churchill Ltd., 104 Gloucester Place, London, W.1.

Biological Future of Man

JOSHUA LEDERBERG

DARWIN's theory set off the historic debate on man's past. Today, with a new biology we mirror his future. Poetry may speak more bravely than Science. However, Policy must rely on Science for an accurate vision of the bounds of human evolution.

MOLECULAR BIOLOGY

Molecular biology has lately unravelled the mechanism of heredity, and we can say that the main features of terrestrial life are within the perceptible grasp of experimental chemistry. Many of its puzzles have already worked out with astonishing simplicity. The basic strategy of life is that of molecular structure. The linear, bi-helical structure of deoxyribonucleic acid (DNA) (and who would have thought that genes would be resolved before tendons?) tells us the mechanism of molecular reproduction—the selection of nuclein molecules that have a complementary fit to the available space on the existing DNA chain. We have also a fair picture of how the nuclein sequence in DNA is translated into the corresponding sequence of amino acids in proteins. And the coiling of the amino acid chain, determined by this sequence, generates the three-dimensional shape by which the protein works. The protein molecules, by a similar fit of shape, recognize one another to aggregate into structural fibres and membranes, or enfold smaller molecules to direct the metabolic flow chart of the cell.

Now we can define man. Genotypically at least, he is six feet of a particular molecular sequence of carbon, hydrogen, oxygen, nitrogen and phosphorus atoms—the length of DNA tightly coiled in the nucleus of his provenient egg and in the nucleus of every adult cell, 5 thousand million paired nucleotide units long. This store of "information" could specify 10 million kinds of proteins. Almost certainly, most of this information controls just when and where some few thousands of proteins will be made—the tendons and enzymes, antibodies, hormones and the like, of which the body is composed.

Evolution is the duplication and exploitation of structural error. Simple organisms have as few as 100,000 units (the even simpler viruses plagiarize the larger genetic "library" of their host cells). Mistakes in molecular reproduction—mutations—are inevitable: one of evolution's marvels is that they are so rare. The innovation rarely serves better; when it does, the cell that carries the mutant DNA will be favourably selected, and the new DNA thus preferentially propagated in future generations.

From principle to detail is still a big step. We do not in fact yet know the actual nucleotide sequence of any gene. Only in micro-organisms, whose DNA content is from a millionth to a thousandth of man's, can we momentarily substitute one DNA molecule for another in the genetic composition of a cell, and then inferentially judge the chemical differences between them. But a little inspiration and reasonable effort will be rewarded by detailed knowledge of genetic structure, very soon for microbes, no more than a decade or so away for parts of the human genome.

EUGENICS AND EUPHENICS

Most geneticists, however they may be divided on their specifications for policy, are deeply concerned over the status and prospects of the human genotype.

Human talents are widely disparate; much of the disparity (no one suggests all) has a genetic basis. The facts of human reproduction are all gloomy—the stratification of fecundity by economic status, the new environmental insults to our genes, the sheltering by humanitarian medicine of once-lethal defects. Even if these evils were tolerable or neutralized or mis-stated, do we not still sinfully waste a treasure of knowledge by ignoring the creative possibilities of genetic improvement? Surely the

same culture that has uniquely acquired the power of global annihilation must generate the largest quota of intellectual and social insight to secure its own survival?

The recent achievements of molecular biology strengthen our eugenic means to achieve this purpose. But do they necessarily support proposals to transfer animal husbandry to man? My own first conclusion is that the technology of human genetics is pitifully clumsy, even by the standards of practical agriculture. Surely within a few generations we can expect to learn tricks of immeasurable advantage. Why bother now with somatic selection, so slow in its impact? Investing a fraction of the effort, we should soon learn how to manipulate chromosome ploidy, homozygosis, gametic selection, full diagnosis of heterozygotes, to accomplish in one or two generations of eugenic practice what would now take ten or one hundred. What a clumsy job we would have done on mongolism even just five years ago, before we understood the chromosomal basis of this disease! No one would undertake a costly programme of animal improvement without a clear cut engineering design from which we could compute the anticipated benefits in relation to the costs.

As further extensions of experimental cytology, we might anticipate the *in vitro* culture of germ cells and such manipulations as the interchange of chromosomes and segments. The ultimate application of molecular biology would be the direct control of nucleotide sequences in human chromosomes, coupled with recognition, selection and integration of the desired genes, of which the existing population furnishes a considerable variety.

These notions of a future eugenics are, I think, the popular view of the distant rôle of molecular biology in human evolution, but I believe that they mis-state its real impact on human biology in the near furure. What we have overlooked is *euphenics*, the engineering of human development.

Development is the translation of the genetic instructions of the egg, embodied in its DNA, which direct the unfolding of its substance to form the living, breathing organism. The crucial problem of embryology is the regulation and execution of protein synthesis which underlies the orderly differentiation of cell types—how some DNA segments are made to call out their instructions and others are suppressed. These issues are now suddenly accessible to experimental analysis. Embryology is very much in the situation of atomic physics in 1900; having had an honourable and successful tradition it is about to begin! But it will not take long to mature. Most predictions of research progress have proved recently to be far too conservative.

Until now, the major problems of human development—not only embryology, but also the phenomena of learning (in its neurobiological aspects), immunity (with its bearing on transplantation), neoplasia and senescence—could be approached at only the most superficial level. They are about to be transformed in the sense that genetics has been, as epiphenomena of protein and nucleic acid synthesis. The present intensity of effort suggests a span of from five to no more than twenty years for an analogous systematization. The application of these advances to human affairs is equally imminent.

On these premises it would be incredible if we did not soon have the basis of developmental engineering technique to regulate, for example, the size of the human brain by prenatal or early postnatal intervention. In fact, it is astonishing how little experimental work has been done to test some elementary questions on the hormonal regulation of brain size in laboratory animals or the functional interconnexion of supernumerary brains. Needless to say, "brain size" and "intelligence" should be read as euphemisms for whatever each of us projects as the ideal of human personality.

The basic concept of molecular biology is the chain of information from DNA to ribonucleic acid (RNA) to protein. We are just beginning to ask questions about mental mechanisms from this standpoint. The simplest and one of the oldest suggestions about memory is the modification of neuronal interconnexion through control of synthesis and deposition of durable proteins at the interfaces. The link between electrical impulses and protein synthesis could easily be the accompanying shifts of potassium and sodium ion concentrations, these ions being

also important cofactors for several enzymes involved in protein synthesis. More elaborate coding, such as the modulations of the actual conformation of the proteins can also be invoked, but may not be necessary to account for the actual storage capacity of the brain. Speculative models for this kind of coding can be built on the basis of present knowledge of protein synthesis, without impairing the conservation of information in the nucleic acids or invoking unsubstantiated principles of electrical control of nucleic sequences. Unlike other cellular systems, the neurones, which rarely if ever divide, need no mechanism to propagate their information to cell progeny. The burden of data storage may therefore be confided entirely to protein.

The purpose of mentioning these speculations is to dramatize the relationship of mental science to molecular biology. The analysis of protein structure and metabolism throughout the brain, the correlation of structural development with learning, its genotypic control, and its alteration in disease are beginning to be attacked in force, impelled in part by social concern for the immensely important problem of mental retardation, as such research must tell us even more about normal mental development.

In another field of developmental engineering Professor Medawar has already exhibited a *tour de force*, the abolition of immunity to transplants introduced in early life, a work which has clarified the biology of immunity and points to the solution of the transplantation problem. At present human individuality is the obstacle to spare-part medicine: the organism rejects grafts from other individuals, even though the alien tissue might be a life-extending kidney or heart. Why the chemistry of our cell membranes should be so individualized is not clear; it may impede the contagious spread of cancer cells, or perhaps of viruses which attack host cell surfaces.

There is little evidence of forethought about the social impact of the solution to the homograft problem, although this solution seems very near and may prove a prototype for the exercise of responsible power in biological engineering. Nor has the full impact of tissue replacement on the practice of medicine been widely appreciated. For example, many therapeutic measures are at present barred or restricted by the possibility of damage to some organs in the course of therapy.

The medical revolution should begin to arouse anxieties over its orderly progress. We must recall that the homograft "barrier" has preserved the personality of the body. We have not hitherto had to think deeply about the technology and ethics of allocating precious organs for lifesaving transplantations. The potential dehumanizing abuses of a market in human flesh are fully anticipated in imaginative literature and modest proposals have been wryly recorded for the furtherance of international trade. Ultimately we must also reserve some concern for the identification of the person: what is the moral, legal, or psychiatric identity of an artificial chimera?

This is an alarmist and ungracious reaction to a gift of life. But we cannot overlook what medical progress has already done for the species in the name of humanity—for example, the catastrophic leap in world population through the uncompensated control of early mortality. We must try to anticipate the worst anomalies of biological powers. To anticipate them in good time is the first element of hope in developing institutional and technological antidotes. Only preliminary suggestions are possible, but even imperfect ones may help to illuminate the possibilities:

(1) Accelerated engineering development of artificial organs, e.g. hearts, which may relieve intolerable economic pressures on transplant sources.

(2) Development of industrial methodology for synthesis of specific proteins: hormones, enzymes, antigens, structural proteins. For example, large amounts of tissue antigens would furnish the most likely present answer to the homotransplantation problem and its possible extension to heterotransplantation from other species. Structural proteins may also play an important rôle in prosthetic organs.

(3) A vigorous eugenic programme, not on man, but on some non-human species, to produce genetically homogeneous material as sources for spare parts. The technical problem of

overcoming the immune barrier would be immensely simplified if the heterografts came from a genetically constant source, the more so if the animal supplying the grafts could be purposely bred for this utility. At present the only adequately inbred mammals are small rodents.

(4) The formal registration of all organ transplants (with some stated exceptions such as blood, patches of skin and similarly dispensable parts that can pose no problems of availability). This would furnish more precise statistics on present efforts at transplantation and help assure an orderly evolution of the technique.

The first three of these proposals illustrate an important gap between academic science and its economic application which too often private enterprise is discouraged or inapt to fill, and which, unlike basic science, calls for detailed social planning.

Man's control of his own development, "euphenics", changes the means and also the ends of eugenics, as have all the preceding cultural revolutions that have shaped the species: language, agriculture, political organization, the physical technologies. Eugenics is aimed at the design of a reaction system (a DNA sequence) that, in a given context, will develop to a defined goal. But will culture stand still merely to validate the eugenic criteria of a past generation? And for a given end, the means will have shifted: the best inborn pattern for normal development will not always react best to euphenic control.

Should biologists give first priority to long-range eugenic concerns of human genotype, or to the gravely imminent issues of human numbers and phenotype: the allocation of intelligence, motivation and longevity?

When euphenics has worked itself out we should have a catalogue of biochemically well-defined parameters for responses now describable only in vague functional terms. Then we shall more confidently design genotypically programmed reactions, in place of evolutionary pressures, and search for further innovations.

Eugenics and euphenics are the biological counterparts of education, a panacea that has a longer but equally contentious tradition. The troubled history of Utopian education warns us to take care in rebuilding human personality on infirm philosophy.

In our enquiry on man's future, the aims of human existence are inseparable from the power and responsibility for human nature. As biological technology dissolves the barriers around individual man and intrudes on his secret, germinal continuity, we must face the issue of a definition of man, taking full account of his psychosocial progeny. We now recognize genetic continuity in mechanistic terms as a nucleotide sequence—in due course this will itself be subordinate to the psychosocial machinery. (Our global experiments on human mutagenesis by chemicals and by artificial radioactivity are the crude, random initiatives.) What will then qualify "man" for the aspirations of humanistic fulfilment, apart from the other robots born of human thought?

COMMUNICATION: OTHER WORLDS AND OUR OWN

In illuminating the chemical mechanism of terrestrial life, molecular biology has completed Darwin's effort at a general theory. This coincides neatly with the technical realization of space flight and of radio astronomy. The challenge of planetary exploration has made us think more deeply about the general principles of earthly life. The prime questions of exobiology, life beyond the earth, concern molecular biology. Do the Martian organisms use DNA and amino acids as we do, or are there other solutions to the basic problem of the architecture of evolution?

How seriously the radio astronomers take the prospects of interstellar communication is hard to fathom. At any rate, there is nothing in biology to discourage the hypothesis of multifocal intelligence in the universe. We have not really thought very much about the problem of finding the *rapport* needed to establish the first contact. It is many times more costly to transmit than to listen, which can lead to a perplexing stalemate in these cosmic negotiations. Hopefully, this technological issue will ripen into a more sophisticated theory of communication

without convention which may have wider interest, as it may also motivate greater investment in the technology of message transmission.

The content of the communication has been least thought about. It might be the greatest help to understanding our own philosophy. How should we epitomize ourselves in telling our story to others? I do not doubt we should describe DNA and proteins, possibly the most arbitrary and unpredictable consequences of cosmic evolution. Technically, the periodic table of the elements would be easy to encode, and would establish chemistry as a context of discourse. But what then? As our presence at this symposium witnesses, man is a communicative animal and it may be some comfort to offer this instinct an infinite challenge.

One prospect may be alarming—that we receive messages that betray our own scientific backwardness. What could erode scientific creativity, so dependent on the delusion of something new under the sun, more than the knowledge that everything is already known but only our access to the oracle is imperfect and costly?

The topic of our symposium warrants other insights, the style and allegorical licenses of the artist; the *verifiable* statements that any scientist might make in predicting man's biological future are probably vacuous. I have been alarmed about my own credentials, which should include responsible appreciation of the relevant science. I could reassure myself that it would be the utmost of human capacity to assimilate a fraction of what others have already said on the same issues, that I was setting myself an impossible task to achieve any novelty of concept or statement. But in acquiescing to this fact do we not now see another image of man's biological future, his future as a scientist?

Today some scientists succeed in assuring themselves of currency in their investigative work, partly through self-delusion, partly through choice of narrowly delimited fields, partly through arrogant but sometimes justifiable assumptions about the incompetence of most of their colleagues, whose papers may then lie unread. A typical weekly reminder list distributed in our department may include upwards of a hundred titles. It would be a more than full-time occupation to digest just this sample of science, and it takes a constant act of judgment to decide what to take time for. The useful output of scientific work has not yet been impaired by the density of "creativity space". In any case, society's return for its investment in science is so great that it cannot afford to hold back from an even greater, though possibly less efficient, allocation of its resources to science and technology. Whether the individual motivation for a scientific career can sustain the pressure on creative opportunity is a perturbing question. The situation is bound to be aggravated by the general increase in population and in the relative popularity of science, perhaps most of all by the sudden accession of the once underdeveloped nations to the main streams of world science.

The problem is compounded by the archaic clumsiness of our basic mechanisms of communication. Man's dilemma is the discrepancy between the size of his population and complexity of his institutions, on one hand, and his individual feebleness, measured as a data input rate of no more than 50 bits per second. The linguistics of the future may improve the technique of speech, or open other channels of communication for our daily needs. Meanwhile it is anomalous how inefficiently science has applied existing technology to tend to its own needs of communication. Incredible to say, within the present system only by chance could I in future discover comments that others might publish in criticism of this very paper. The phenomenon of science has only recently attracted the analytical interest that can help to expose such anomalies. Until it has gone much further we can only guess at their roots in personal and cultural psychology. They do lend support to the hypothesis of unconscious resistance to effective, and therefore perhaps disturbing, communication.

The changes in the scope of research have changed its quality. Research is the effort to add to *human* knowledge. The extent of existing knowledge was hitherto more readily discoverable:

contributions were less competitive, did not need endless persuasion and repetition to be heard; the challenge was the struggle with nature. The complication of science has made it inexorably more human—or should we ever have forgotten this limit to objectivity?

Man's future as a biologist surely depends on the rationalization of scientific communication. Society makes many demands on the energies of the global community of science. We must also take care to look to the preservation of our own future by the modernization of our own techniques for efficient but free expression.

The theme of this paper was to have been molecular biology, the transfer of information from one macromolecule to another. It has become an essay on communication, under the same logic by which man has evolved from substance to concept.

BIBLIOGRAPHY

1. Huxley, J. (ed.) (1961). *The Humanist Frame.* London: Allen & Unwin.
2. Lederberg, J. (1958). *A View of Genetics.* Stockholm: Les Prix Nobel.
3. Medawar, P. B. (1959). *The Future of Man.* London: Methuen.
4. Muller, H. J. (1962). *Studies in Genetics.* Bloomington, Ind.: Indiana University Press.