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The future of man

by

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I have always looked upon essays on man's future as a hobby to be turned to in one's declining years, so it was with mixed feelings that I received your invitation to speak on this topic. Certainly the essays on the future of man with which some of our distinguished colleagues have amused themselves are most enjoyable, for example that of Hooton on "The Bright Past and Dim Prospect of a Tottering Biped" or Shapiro on "Man 500,000 years from Now".

The classical approach

One of the ways in which our speculative predecessors approached the topic was by looking backwards, enthusiastic as they were over the abundant new material that was coming from the human fossil record, from the comparative study of primatology, and from a variety of other sources, and that gave some indication of the biological past of our species. The features differentiating man could only have emerged as the result of long-term trends. Applying the principles of uniformitarianism enunciated by Lyell for geology in the mid-19th century, by which processes now going on are the same in kind, if not degree, as those in the past, it was a simple error to assume that past trends could be extrapolated forwards.

For example there was the reduction of body hair and its curious retention in the most unexpected regions ; side effects of this perhaps were (a) a stimulus to inventiveness of gadgets to shave with, ranging from the primaeval flint to a modern miniature lawn mower, and (b) instruction in wasting time, for a modern man has perhaps dissipated over 3000 hours shaving by the time he reaches the age of 70. There are the numerous anatomical changes consequent upon his curious posture and gait — the elongation of the legs, the knobby knees and razor-crested shin bones, the degeneration of the little toe and the lack of grasping ability of the hallux, the tilting of the pelvis and its broadening, all of which stemmed from those earliest ancestors who attempted bipedal gait and upright posture, on an increasing number of occasions, for what purpose we shall never know, and became increasingly proficient in it. The swollen brain case, the dwarfed face, the reduced

dentition and jaws, accompanied by the development of speech, reduction of olfaction, apparent increase in intelligence, all these are clear trends over the last million or so years.

Yet in the more recent phases, by comparison with the anatomical features of the upper paleolithic dwellers, there has been very little evidence of evolutionary improvement. The brain has not increased in size — if anything it has become smaller. The spine has not improved its curves ; the pelvis is still a source of weakness. Indeed, there is clear evidence of further anatomical degeneration. The jaws have continued to shrink until they are too small to accommodate the permanent teeth, and indeed may not match each other. The nasal skeleton has continued to contract.

Shapiro suggested that men will become taller, primarily because of the secular trend that has been discernible in the present century but, as Howells pointed out, early members of *Homo sapiens* were all roughly of modern size and indeed the Cromagnons were apparently taller than most Europeans of today, so that the present secular trend in Europe and elsewhere is only a recent sudden fillip as a result of the "hot house" environment of modern life with its better food and medical care ; this will reach its limits before long, and in any case man cannot afford to become gigantic on account of the additional skeletal and soft tissue strains induced and the accompanying loss of efficiency. Brains are unlikely to become larger, for the present size has already complicated the process of childbearing, and indeed brain size today appears slightly less than in the upper paleolithic. There are still the weaknesses associated with upright stature which require to be perfected, the design of the lumbar region, the weaknesses of the legs and circulatory system that become so apparent in older age. Long heads, a relic of the day when face and neck muscles had more effect on head shape than did the brain, will continue to be replaced by increasingly round ones, while the face will become more sunken, noses higher and chins more pointed. The third molars will probably disappear quite soon, since they are already so variable, so will our little toes and toe nails, and probably also our hair. Such olfactory sensitivity as is retained will probably diminish further — in the light of the modern trends of overcrowding this may well be desirable — and the same holds for delicacy of hearing in view of the massive barrage of noise with which the modern human ear is assailed.

The visionary's view

So much for ideas of the professional students of evolution. To take a different view, let us look at the writings of a novelist of about the same period.

In 1932 Aldous Huxley wrote "Brave New World". In the population envisaged there, there was recognition of distinct classes of individuals (alpha to epsilon). All children were created from ova removed from the mother, inspected for abnormalities, and then immersed in a warm bouillon of spermatozoa to fertilise them. The ova were then placed in the incubator where the alphas and betas remained,

while the gamma, delta and epsilon eggs were brought out after 36 hours to undergo the "Bokanovsky process" ; in this, exposure to x-rays induced buds to be formed, each of which was allowed to develop individually, so creating scores of identical individuals. The eggs of all classes were then transferred to bottles where the environment was carefully controlled according to the class of being the egg was to develop into. Complete science fiction when it was written, and paralleled by many since.

Appraisal

In these two approaches it is the bizarre that immediately attracts attention. It is only upon reflection that one appreciates the real difference. In the first, man's genepool bobs like a cork on the waves of chance, drifting at the mercy of random events and directed only by the currents of selection. In the second, control is paramount — control of quantity, control of quality. For the first time is there the suggestion that man may control and direct his future.

Both sets of views were written before the recent great interest in and development of genetics, particularly human. In the light of modern genetic knowledge, forecasting of anatomical trends on the basis of extrapolation from the past does not appear feasible, for the factors and processes bringing about the trends require first to be identified and then their continuation assured in order to produce the suggested effect. But by contrast how close to feasibility was Aldous Huxley! Attitudes have already changed to the extent that the need to control numbers is widely accepted. Certainly man is today much more aware of the importance of genetics and its consequences, of the nature of genetic variability, and of the fact that individuals are by no means equal in their genetic constitution. Many of the techniques envisaged in "Brave New World" have been developed, improved upon, and superseded. The removal of ova from a woman and their extracorporeal fertilisation has been achieved. So incidentally has been their subsequent reimplantation leading to the birth of children. Improved methods of culture have led to great recent success in routine fertilisation *in vitro* of eggs of small mammals such as the mouse, hamster and guineapig though not yet in man. This has been accompanied by increased control over preimplantation development so that in some species, e.g. mice and rabbits, life can be supported in culture to the morula or blastocyst stage, and surgical transfer to the recipient females is followed by rates of successful subsequent development to viable young similar to those that occur in natural pregnancies. Many mammalian offspring from such procedures have been examined, and in very few cases is there any suggestion of an embryopathic effect ; indeed in these very early stages there appears to be appreciable resistance to malformation, even if groups of cells are removed, and such damage is often repaired ; it appears easier to destroy the embryo than to cause malformation at these early stages. Thus there is time for intervention in the genetic instructions of

the embryo, and such intervention need perhaps only be applied to a few cells to exert a considerable effect. The modification of the genetic material through genetic engineering is so close at the research level that in many countries government control bodies have been set up to monitor the researches. For example, in Britain there is the voluntary Genetic Manipulation Advisory Group, in the USA the guidelines issued by the National Institutes of Health and more forceful authority is in process of preparation, and in at least nine European countries committees to monitor research have been instituted. The object of all these bodies is safety, to prevent biological contamination by dangerous genetically new organisms, rather than to control and direct experimentation.

Genetic engineering

In genetic engineering there appear at least four possible approaches :

Transduction, the virus-mediated transfer from one cell to another of genetic material. Transduction is already reported to have occurred in humans. The *Shope Papilloma* virus which causes tumours in rabbits also induces the synthesis of a distinctive form of the enzyme arginase, which lowers the concentration of arginine in the rabbit's blood. Blood specimens from subjects who had worked with and therefore been exposed to this virus, as compared with those from random control individuals, had lower arginine levels, were carrying "virus genetic information", and had specific antibodies against the distinctive form of arginase, suggesting that the virus DNA had supplied the information for its synthesis. The *Shope Papilloma* virus is a harmless "passenger" virus in man and thus is a candidate vehicle for planned gene introduction. So too are strains of Simian virus 40 (SV40). Such applications are a long way in the future but eventually it may be possible by genetic surgery using restriction endonucleases to extract from normal human cells the sequence of DNA that was missing from or was wrongly made in a patient, isolate it, use it as a template for the synthesis by bacterial enzymes of numerous replicates of itself, incorporate the synthesized gene into the genetic medium of a suitable virus vehicle which in turn will transfer the new gene to cells throughout the patient's body and precisely replace the faulty gene.

Transformation, the incorporation of a segment of DNA from one cell into the genetic material of another cell. It is already reported that human cells in tissue culture may be transformed ; the ability to synthesize isosinic acid pyrophosphorylase has been transferred to cells that lacked this capacity by the application of DNA containing the appropriate genetic information. Thus it may be feasible in the future to treat a germ cell defective in some gene function with DNA from one known to be sound in that respect.

Directed induction of mutations at specific loci on the chromosome. In microorganisms it is possible to produce mutations in a nonrandom fashion by the use of

chemical mutagens, such as synthetic molecutes related to nucleic acid bases. These are incorporated into DNA and upset the replicative process so as to cause the replacement of the original natural base by another one, thus producing a mutation. It may well be possible in the future to eliminate a genetic defect by this method to obtain a reverse mutation from the deleterious to the normal allele. Another potential approach to directive mutation is through the synthesis in the laboratory of a desired molecule of DNA. Such a tailored DNA molecule, if it can be isolated in pure form from a cell, can be replicated by already known enzymatic processes to any needed quantity. This new gene can then be introduced into the mammalian cell in culture, as in bacterial transformation. If a rare transformed cell could be selected and cultured the new cells could be transplanted into a living organism to correct a defective function of the original host, and if the host's own cells were used in the culture, then one would avoid the immunological difficulties.

Nuclear fusion of somatic cells. This form of genetic manipulation is based on the discovery that tissue culture cells can be fused by treatment with Sendai virus, one of the influenza group of viruses. Cells from different species can be brought together so that the nuclei from both are dividing in the one cytoplasm, and if divisions are synchronised the two may combine to produce a single nucleus. This technique is particularly useful in gene mapping, but its potentialities for combining a cell from an affected and unaffected individual to produce a "normal" gene complement is clear.

There is a great difference between on the one hand tha development of new techniques and their application in further laboratory research, and on the other their application in practical large scale reproduction of domesticated animals and man. The first difficulty is economic; the techniques are expensive and time-consuming, and nature's methods still remain the cheapest. The techniques are not always amenable to massive implementation and moreover require skilled laboratory workers who are scarce. Their possible applications to man involve a host of ethical, legal and other considerations which are not yet resolved, and indeed are barely stated; but there is obviously a case to be made for their application in specific individuals, as is other surgery, and this is likely to meet with less resistance than bulk interference with reproduction. Though when one considers the enormous change in western reproductive patterns over the last century, and the methods that are today available for mass indoctrination, this too may well come to be.

The final process of Huxley's vision, the control of the environment of the developing individual in order to improve the manifestation of his genetic potential, is already with us on a limited scale. Individuals who will suffer from phenylketonuria and galactosaemia can be identified soon after birth, and carefully controlled diet restricts their intake of phenylalanine and galactose respectively, so that these do not build up into toxic levels as the result of the patient's metabolic defect, and the disorders are avoided. As regards the internal milieu, diabetes is controlled

by injections of insulin, and there are many other such examples. In these the expression of the genetic information is altered so as to reduce its deleterious effects, and as our understanding of the regulation and control of gene action increases, many other applications will become available.

But these and other techniques are still largely in the experimental laboratory, and it will be many years before they can be applied practically on a large scale. The period of excitement about the breadth and imminence of genetic engineering was certainly premature, and it is today realised that its applications lie in the more distant future. Its chief value will then perhaps lie in supplying genes, perhaps by viral transfer, to people carrying deleterious mutants, or to remove cancer cells. Certainly the application to changing the genepool of human poulations is very restricted indeed. What these developments have shown us is that the genetic advances to be expected in the future are beyond our imagination, just as present research procedures were beyond the conception of scientists a generation ago. But of course to implement these advances, it is necessary to ensure that civilisation continues and that we neither starve ourselves nor crowd ourselves off this planet.

The modern dilemma and its solution

Man has however already made considerable impact on his genepool as the result of developments over the last few centuries. The gene frequencies in the world's population of 2000 years ago were very different from those today, largely because of the enormous population expansion of the European peoples and their expansion overseas, so that the genes characteristic of the early European populations now make a major contribution to the frequencies in the species genepool. Also, the changing pattern of medicine over the last century or two has meant that the genes which conferred resistance to the infectious diseases have lost their survival advantage in western society largely as the result of modern knowledge of drugs and hygiene. Today deaths from typhoid fever or whooping cough or diphtheria are negligible in numbers by comparison with what they were a century ago. One can expect that such genes as are involved in such resistance will diminish in frequency with the relaxation of their selection advantage.

There is another cause for concern, again as the result of modern therapeutic methods. The apparent dilemma is that we are salvaging a number of patients with genetic disorders in the present generation who would otherwise have died, are retaining their genes, and this is at the expense of future generations. A child born in 1867 and developing retinoblastoma had a 5% chance of surviving to adulthood and passing on the retinoblastoma gene. A child born today has a better than 95% chance of surviving. One can expect therefore the frequency of the retinoblastoma gene to increase ; already there is a strong suggestion that the incidence of the disorder has doubled in the last generation. Similarly, haemophiliacs at the beginning of this century were estimated to have a fitness of only 28%. Today as the

result of modern methods of treatment, the fitness has increased to approximately 80%. Again the gene frequency can be expected to increase. The frequency of haemophiliacs in England in the 1930s was approximately 1 in 11,000 male births, whereas today the figure is about 1 in 7,000 and the figure will increase to a new equilibrium of approximately 1 in 3,500. Already the load of deleterious genes in man is high ; approximately 1 in 40 of all liveborns suffer from a serious genetic defect, a genetic disorder is implicated in the deaths of over one-third of all who die in childhood, and then there are all the genetic disorders which develop in middle and later life.

People in the west are now much more aware of the nature and importance of genetic disease, and in Britain and a number of other countries this has been recognized by the large increase in genetic advisory clinics. Here any who are concerned about genetic disorders in their family history and the risks of such disorders to their children can seek advice. In such clinics complete family histories are taken, full investigation carried out to confirm the diagnosis where necessary, and the risks advised. Where relevant, antenatal diagnosis, selective termination of pregnancy, carrier state detection, and other such procedures are drawn to the attention of the enquirer, and always it is left for him or her to make the final decision.

Thus, instead of the old concept of improvement of our genetic heritage by compulsory sterilisation or inflated (even enforced) reproduction, today the eugenic approach is seen as a part of preventive and family medicine. Integrated into the National Health Service in Britain, it provides a service whereby besides providing information, the enquirers can subsequently be directed to any of the practical procedures that they decide on — prenatal diagnosis of those defects which can be so identified, pregnancy termination, adoption, contraception, artificial insemination. In this way each individual resolves the ethical problems for himself — there is no compulsion. But what is the longterm outcome likely to be? Does it resolve the problem of increasing frequency of deleterious genes from salvaging the affected individuals?

Many a patient feels that since he owes his survival or that of his affected child to medicine, and hence to society, he can perhaps repay the debt by restricting his own fertility. Certainly we know that restriction of fertility is similar in its genetic effect to nature's more brutal method of production of many children followed by mortality of the affected. If all individuals with known seriously deleterious genes restrict their fertility to a level lower than the average for the population, then there will be no great rise in deleterious gene frequency and it may well be contained. The same argument is applicable to the effects brought about by the selective abortion of homozygotes with an autosomal recessive disease, which would normally preclude survival to adult life, for this encourages compensatory replacement by a phenotypically normal child who, in two cases out of three, will be a heterozygote capable of transmitting the deleterious allele to future generations. The same applies after abortion of an abnormal fetus from a parent with a balanced translocation, for in

compensation there may come phenotypically normal children who in one case out of two will have a balanced but abnormal karyotype, who again can transmit the abnormal chromosome. Responsible restriction of compensatory reproduction will go far to contain the resulting increase in deleterious genes or abnormal chromosomes. In practice such events do tend to restrict the number of children subsequently produced, so that the contribution to posterity is less than might at first appear.

In the treatment and prevention of genetic disease in the individual and in his family, as in other branches of medical care, it is imperative to use whatever methods are to hand. The effect on future generations is for the patient himself to consider, not for any dictatorial outsider, though information about the effects of reduced instead of zero fertility can often give renewed hope to the more responsible enquirer concerned about posterity who in his ignorance may have intended to renounce normal family life. Moreover as the present discussion has indicated, technical achievements have been rapid, and new advances in the near future may well lead to the supercession of many of the present methods of dealing with genetic problems, and this realization also can bring hope to the patients and their families.

In meeting the dilemma, then, it is by adopting the point of view advocated here, by locating genetic advisory work firmly in preventive and family medicine, that we can help to plan the future, to ensure the retention of the right values as well as the right outcome. For a future we can look forward to, in a planet that is not too overcrowded, we need to retain the individuality of the individual and the personality of the person to avoid the loss of the humanity of the human. By so doing we go far to achieving this end.

Summary

Classical essays on man's future attempted to extrapolate past anatomical trends into the future. This is fallacious. The visionary's approach is unrealistic and uneconomic, but nevertheless foresaw techniques many of which are today feasible in the research situation, and the possibility of control, both of quantity and quality. Genetic engineering, involving transduction, transformation, directed mutation and nuclear fusion, gives promise of rectification of some transmissible defects. These techniques are unlikely to have wide effect upon population genepools but may be of considerable value in dealing with particular hereditary problems of individuals. But man has already unwittingly altered his genepool, by dismissing genes advantageous in an earlier environment and retaining others that are deleterious, and is continuing to do so at the expense of posterity. Development of genetic advisory centres with the relevant supporting services provides a realistic and humane resolution of this modern dilemma.

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