
The Challenge of Life

Biomedical Progress and Human Values

Roche Anniversary Symposium

Reprint

Biomedical frontiers: genetics

by JOSHUA LEDERBERG

From time to time during the past decade, I have been challenged to collect my thoughts about the human implications of advances in genetic research. My first reactions were typical of those of many of my colleagues when they first looked up from the laboratory bench. Suddenly all things seemed possible – and on an earth which lies between heaven and hell, this prospect is at best ambivalent.

One can catalog the most plausible technical options, and I will not shirk this part of my task (see Table 1). However, to do only this almost inevitably leads to misunderstandings and misattributions. Furthermore, our forecasts will be factually wrong if they do not take account of the cultural setting, as well as the scientific bases, of health research and its applications.

For example, I once offered what I thought was a safely ironic formula: ‘given sufficient time, any enterprise (including the renovation of man) would become possible, provided it did not violate some basic law of physical nature’. Long before we had mastered interstellar transportation and taught computers to write good poetry, we would surely have eliminated death; and genetic engineering would be a closer step on the same path. *Given sufficient time* made the formula safely tautologous. Even so, it conceals latent assumptions – that the human enterprise will continue, and that it will encompass an enduring commitment to scientific inquiry and its application to health and economic efficiency.

I did not then seriously doubt that scientific work would continue to double every twelve or fifteen years. Its internal information flow might nevertheless be overloaded, and the integrity and efficiency of the careers of individual scientists might become the limiting factors in the overall growth of knowledge. (Innovation cannot outpace the rate at which basic tools are formed and shared with the oncoming generation. Thus, if a language were to evolve with accelerating speed, we should perforce end up with Babel, or no language at all.) I did not foresee the extent to which the underlying commitment to progress would be rejected by a significant counterculture.

Science and technology are among the pre-eminent targets of this nihilistic revolution, and with good reason. The movement is a revolt against large-scale social organization (held responsible for imperialism, war, pollution and de-

humanization), and this is inextricably interdependent with science and technology. The modern industrial state, east or west of the Elbe, rests upon efficiency of production by scientific techniques. And science can hardly be funded except from the surplus. Yet scientific criticism is also the most revolutionary source of skepticism of the values of industrial capitalism.

Medical progress is by no means immune to similar criticisms. We will hear that it is fundamentally immoral to waste resources on the development of new treatments in the face of world-wide needs for elementary hygiene and nutrition. (The same critics may even attack programs for eliminating smallpox, on the grounds that this will simply expose more children to kwashiorkor). At a more sophisticated level, many physicians approach a philosophy of therapeutic nihilism, wondering at what point new drugs may be doing more harm, overt or unsuspected, than good. In this vein, it is likely that there will be fewer drugs in tomorrow's repertory than today's; that much more pharmacological effort will go into more complete validation of existing agents, including many that are widely used with or without the benefit of professional prescriptions.

Against such a backdrop of existential confusion, it is hard to generate much enthusiasm for a brave new world – but the same skepticism also helps to reduce the odds that innovations in the genetic sphere will be rapidly and uncritically adopted. We need no longer repeat the caveats about rigidifying human values that the early eugenicists had taken for granted. Like it or not, we face a world that is almost perversely pluralistic in its basic values. Even in the most intellectualized communities, genes for genius are likely to be as little sought after as special schools for gifted children – perhaps out of folk wisdom about the little we know, and the less we do, about the ideal education for a given child.

The insularity of the eugenic advocates is equally quaint. The evolutionary impact of the most ambitious programs of selective breeding, sperm banks, or other plausible technologies, could not begin to compare with the shifts of global population that are connected with political and economic development. Those who are concerned about the future of man will have to pay more attention to the condition of the overwhelming majority of contemporary men. The human gene pool is very poorly represented in this room.

Although the powers of scientific wizardry are too often exaggerated, the present congregation does have a special leverage on global health, nutrition and some aspects of population control, and world peace. We are part of the most nearly bona fide international community – of health and scientific workers. And if, by our personal example, we cannot demonstrate alternatives to the nation-state as a medium of personal growth and expression, who will?

The remaking of man is then an impossible and inappropriate framework for the application of genetics. Genetic science could shed light on the evolutionary diversification of the species. But what has emerged so far is the almost enigmatic lack of reliable evidence for consequential systematic, biological differences – related or comparable to the diversity of culture – among the

racess of man. This may say more about the crudeness of our tools than the realities of differences in temperament. But it is mainly a testimonial to the wide variation of types that make up every culture, and make every generalization dangerous.

A few critics of objective research have criticized the very effort to discover genetic differences between races. In part, this is a reaction to the indefensible prejudgments about such research that have been offered by SHOCKLEY^{3,4}, with which I need hardly say I am in violent disagreement. These critics go further in suggesting that inquiry into racial difference can have no humanitarian justification – but this is also an implicitly racist prejudgment. Much of the controversy is based on mere ignorance of the significance of the term ‘genetic’, which is misrepresented as ‘irremediable’. Nothing would be more helpful in achieving equality in opportunity and in education than an understanding of *specific* genetic and developmental mechanisms in intelligence and in the learning needed for survival in modern society.

For an extreme example, until we knew how to teach the congenitally deaf to communicate, the deaf-mute was de facto an idiot. We have only the vaguest knowledge of the subtler variations in cognitive style among children, including the all-important factors of timing and balance. Hypothetically, a child who might be an excellent reader if taught by a particular technique at age eight may now be labelled a failure and discarded at age six.

Racial variations – so heavily overlaid with confounded environmental factors – are the least promising material for such investigations. Studies *within kindreds* of F-2 hybrids would be advocated by any geneticist, but have not yet been taken up.

The principal task of genetics is scientific *understanding*; and the principal target for its applications to man is the alleviation of individual distress – which the physician cannot repudiate no matter what the general state of the world. In pursuing his goals, it should go without saying that the geneticist is bound by the same set of ethical restraints that apply to other innovative branches of medicine. The surgeon does not use his scalpel by whim; and even in the chase after potential knowledge he is, above all, accountable by law and ethical tradition to the needs of his patient. There is of course some risk that a totalitarian regime will find it convenient to lobotomize its captives, or perpetrate the equivalent through controlling and disseminating genes, or drugs, or circusses, or even songs (as Plato boasted). This fear may be one of the impelling motives of the anarchistic movement. But liberal paralysis and self-denial have an unenviable history of failure against totalitarian ruthlessness.

Table 1 catalogs a number of potential techniques that may relate to the prevention or therapy of genetic disease, or which may influence genetic constitution. This is not a well-bounded arena, for all of medicine – indeed all of culture – is potentially euphenic. That is they may (1) ameliorate the actual development and expression of genetic predisposition, and (2) thereby indirectly influence the relative frequency of different genes in the population. This dis-

cussion must also overlap the medical applications of embryological knowledge, for many genetic defects will have to be prenatally diagnosed and treated to forestall irreversible failures of development, which then result in lifelong impairment.

The boundaries of genetic disease are also uncertain, for every pathology must have both a genetic and an environmental component. Many common diseases, as well as overall longevity, have a significant heritability. About five percent of overall morbidity can be related to specific genetic defects with a relatively simple basis; if we also take account of the heritable component of prevalent diseases like schizophrenia, diabetes, cardiovascular disease, and so on, at least a fourth of total morbidity (in medically advanced communities) must be attributed to genetic imperfections.

Genetic load, mutagenesis and environmental hygiene

The genetic load is therefore a formidable part of the problems that must be faced by medical practitioners and their patients. Plainly, preventive measures should have a high priority, if we could thereby prevent the intrusion of genetic defects in the first instance. This may not always be possible – an unknown part of the genetic load is ‘segregational’, that is, it derives from a relative disadvantage of either of the homozygotes compared with a fitter heterozygote. Natural selection then tends to keep both of the alternative alleles in the population, notwithstanding the inevitable quota of impaired homozygotes that must recur at every generation.

However, the ‘mutational’ part of the genetic load must be considerable, and this is related to the rate of mutation (informational deterioration) in the genetic material. A certain level of mutation is an inevitable byproduct of molecular accidents in cell metabolism. However, if we argue from the relative incidence of environmental compared with intrinsic carcinogenesis, which may be a parallel phenomenon, we may judge that four fifths of our ambient mutation rate is of environmental origin, and could be eliminated by environmental hygiene (relating to drugs, food additives, and possibly some natural foods, water and air pollutants, certain virus infections). About ten percent of that quota can be attributed to the natural radiation background, which is essentially not avoidable, and an equal proportion to artificial radiation (mostly incidental to diagnostic X-ray), much of which is avoidable.

This issue has been prominently displayed as an argument against the frivolous use of LSD (especially of ‘street grade’); but equally cogent evidence against cyclamates and trenchant suspicions about many other widely used drugs have been ignored.

Here is a field full of confusion with respect both to policy arguments and to the technical assessment of mutagenic hazards. I believe environmental hygiene may be the most fruitful area of application of more sophisticated molecular genetic analysis.

Options for genetic therapy

Among these options, a few stand out for offering the most realistic opportunities for health benefits. They include:

Antenatal diagnosis. An increasing number of diseases will be reliably diagnosed by cytological and biochemical studies on cell cultures derived by amniocentesis. We have already made exciting advances in the understanding of several neurochemical disorders, which rely upon the identification of specific enzyme defects. The techniques of cell-fusion and of chromosome identification with fluorescent stains will strengthen our ability to trace mutant genes and similar methods will also help to identify high-risk parents. We can also visualize more direct assays for specific information content of DNA with techniques for the isolation of specific messenger RNA, and then of the homologous genes. The DNA segments can then, in principle, be tested in cell-free systems for protein synthesis, or perhaps even subjected to direct analysis of their nucleotide sequences. This level of sophistication in the analysis of gene effects should, in many cases, lead to deeper understanding of the disease, and may provoke explicit therapies. Meanwhile, our main recourse is voluntary abortion of the impaired fetus, to allow a mother the best chance available to her of delivering a child free from malignant defect.

Our experience with the antenatal diagnosis of sex should help correct overanxious predictions about the anticipated misuse of 'genetic engineering'. This has allowed a reliable method of voluntary control of the sex of offspring for some years. Whether the sex of the fetus has ever been a controlling factor in a decision for abortion, without more persuasive indications, it simply has not surfaced as a significant social problem to warrant any special regulatory controls. The common-sense and patient-oriented values of the medical profession remain the most effective bulwark against nonsensical distortions of its tools.

It has been suggested, quite seriously, that voluntary control of the sex of offspring might encourage a limitation of family size (e.g. one boy, one girl) consistent with the social interest in overall moderation of population growth, and that a balanced sex ratio would be maintained even under voluntary choice. In any case, keeping the state out of reproductive decisions altogether is a safeguard against undue interference.

Geneticists are perhaps fortunate that the revolt against 'sexist chauvinism' has taken hold before their techniques could be blamed for these cultural shifts in life-style, which so outweigh the influence of medical practice.

Transplantation. Many genetic defects involve cell populations as metabolic units that could be supplanted or restored by transplantation. For example, complete transfusion plays an important part in the therapy of Rh-hemolytic anemia (but is associated with a danger of graft-versus-host immune disease when applied to the fetus). The scope of tissue transplantation should not be judged by its present limited application, which is constrained by the hazard of graft-rejection. Specific ways of mitigating rejection are bound to appear as

a fruit of immunobiological and immunogenetic research. We will then have a simple, practical way, for example, to deal with sickle-hemoglobin disease, namely by transplantation of normal erythropoietic marrow to the newborn, or perhaps the fetus. We will also surely find that many other diseases, genetic or not, are amenable to relief by tissue and organ transplants – e.g. hepatocytes for phenylketonuria and for galactosemia, or insulin-secreting cells for diabetes. The last example illustrates the opportunities for therapy even where the transplanted organ may not be the primary seat of action of a defect.

Transplanted immunocytes are also likely to play a key role in the treatment of auto-immune disease (perhaps after systemic elimination of offending cells) and in the prevention and treatment of neoplasms.

In cell biology research, we have just begun to move into the arena of systematic work on the genetics of somatic cells. The discovery by Henry Harris (Oxford) of powerful methods to induce the fusion of cells has attracted enormous interest in the consequences of mixing chromosomes of different genotypes and species, and in their reassortment in various combinations. The way is then open to genetic analysis (and genetic engineering) of mammalian and human cells in a way that would have been technically and ethically impossible otherwise. We can then also expect that domesticated lines of somatic cells will be important inputs to therapeutic applications of transplants.

Vaccination and virogenic therapy. Since 1798, vaccination has constituted an important medical application of the genetic modification of somatic cells by viruses, though its practitioners to this day are often oblivious to it. Jenner found that inoculation with infectious lymph caused a mild disease, cowpox, immunity to which also protected against the dangerous smallpox.

Many aspects of vaccination are still scientifically obscure; but we can now describe the process in terms of molecular genetics.

The DNA of the cowpox virus is purposely introduced into certain cells which adopt the genetic information contained therein. These cells thereupon produce new gene products, encoded by the viral DNA, which stimulate other body cells to produce antibodies against them. The cross-immunity is then a byproduct of the virogenic alteration of some cells of the host.

Live viruses are now widely used for vaccination against many other diseases, including polio, measles, and in special cases or in the near future, rubella, mumps, rabies, and so on.

Vaccination can be regarded as if it were a therapy to replace the functions of hypothetical genes not normally present in the human organism, those that would endogenously stimulate the formation of antibodies. This idea can be extended, in principle, to other gene products, for example enzymes that may be missing in certain gene-defect diseases like phenylketonuria and perhaps diabetes. Laboratory models for this kind of virogenic therapy are being perfected, and rational trials for human disease can be anticipated shortly. Although basic genetic principles underlie this technique, and the genetic apparatus of somatic cells is altered, it is classified as euphenic because the germ cells

are left unchanged and there should be no effects in future generations. This is a matter of empirical observation, rather than a necessary principle in biology, and it is quite conceivable that some inoculated virogenes might also be inherited, as has already been postulated for certain tumor viruses in rodents. This reservation applies with equal force to vaccination against infectious diseases, about which we have little information in proportion to the enormous numbers of children involved.

The recent discovery of 'reverse transcriptases' which copy RNA information back to DNA promises to simplify some of the technical problems of developing virogenic agents. Differentiated cells should, under certain conditions, produce multiple copies of active, messenger RNA molecules, and it will be easier to purify and test these than to attempt to dig out a single DNA gene from the complete chromosome set. (In due course, however, this should also be facilitated by knowing the chemical signals that distinguish the active from the inactive genes in a given cell.) Reverse-transcription would then allow the recording of the RNA-message into DNA, which would then be spliced to a virus for facilitated re-integration into chromosomes.

Virogeny will be in competition with cell transplants for the restoration of genetic defects; but each may have special advantages in particular cases. For example, the transplantation of neurones is not likely to be very helpful except at the earlier stages of development.

The introduction of virogenic therapy should reawaken our concerns about vaccines intended for immunization against infectious disease. As we become properly attentive to the problems of unexpected side effects, we may find it necessary to devote more careful attention to the prophylactic agents used on a mass scale than to virogenic therapeutics applied even at some risk to a few badly impaired children.

Renucleation (cloning). From the work of BRIGGS and KING¹, and of GURDON², we know that an activated egg may be renucleated with a nucleus taken from a somatic cell of an existing frog. From a genetic standpoint, the new embryo is comparable to a cutting, or clone, of a rose plant.

The technical possibility of renucleating the human egg may then be an achievable extrapolation of work in progress with laboratory animals, and is likely to be reinforced by emerging utilities with livestock. Does its potential availability for human reproduction pose any special difficulties or opportunities?

This question was introduced first to make a rhetorical point. Many speculations had been forwarded about the possibilities of 'genetic surgery' of a kind that would require fantastic innovations in our knowledge of molecular genetics. Renucleation had, however, been demonstrated long since in frogs; and it was also very plain that it would be available in man as a necessary prerequisite to more incisive techniques of genetic manipulation. It follows that, *if* one wishes to agonize about the likelier directions of futuristic change, one should attend to renucleation.

If it could be done today, it is hard to see where renucleation would have

very important applications; but this is precisely the kind of anticipatory study that needs to be done. On the positive side, it may give some otherwise sterile mates the opportunity of parenthood. An anovulatory woman might borrow an otherwise wasted egg cell, renucleate it with one of her own, or her husband's, somatic cells, and have it reimplanted into her own uterus. Or a fertile wife might offer an intact egg for microsurgical fertilization with a haploid spermatozoan nucleus from her azoospermic husband.

We can properly understand the moral objections and justifications of such procedures only if we explore the whole continuum of technical interventions in human reproduction. Ever since primitive man discovered the connection between sexual intercourse and conception, human reproduction has entailed deliberate exercise of purpose and intelligence, an unavoidable power and responsibility for the next generation. The guarding of such responsibilities against external intrusions is the essence of personal freedom. It goes without saying that we would abhor state-enforced reproduction of any kind. Conversely, to what extent should individual patients be deprived of the possibility of using technical devices they, and their professional counselors, believe to be in their own and their offspring's interest?

Many unanswered questions remain on the ethical or technical merits of renucleation. Popular discussion of cloning has probably overemphasized the significance of a common genotype: monozygotic twins are not copies of an identical personality, especially if they have been reared separately. They do resemble one another more closely than other relatives, to be sure; and renucleation could be a means of avoiding certain genetic defects that arise from segregation. If, for other valid reasons, renucleation is ever practised, we can clean up many uncertainties about the interplay of heredity and environment; and students of human nature will not want to waste such opportunities. So many developmental hazards may be associated with renucleation, that very extensive animal studies would be the minimum prerequisite to ethically justifiable trials in man, and the interval gives us ample time to ponder the values in balance. It is easy sport to write fantasies about the possible extrapolations of any scientific advance. What fantasies could be derived from the surgical division of a brain into several barely communicating parts! Useful counsel to policy makers should go beyond these explorations. Special attention must be devoted to the social factors that must prevail to launch a technology, then for this to 'go out of control'. The nuclear arms race is the prototype – but the pressures of international conflict make this an egregious example. No other technology can command more than a fragment of the military budget, and biology will have a long way to go to approach the auto industry and market. In my own view, the struggle to prolong life at all costs, and our partial successes are already creating ethical and social dilemmas far more grievous than the innovations of quality control of births. The economic impulses for life-prolongation are theoretically unlimited, empirical evidence of carelessness in personal hygiene notwithstanding.

Our consensual standards of an ethical medical experiment require that it serve a reasonable humanitarian purpose and that it have the informed consent of the individuals concerned. The problem of renucleation sets into relief the general problem of parenthood. Who else can speak for the welfare of the individual not yet in being? Should parents be held in contempt if they procreate by natural means in the face of risks of a significant deformity in their offspring? Should they be encouraged to undertake artificial measures that will give their young an easier start? And where is the boundary-line of the responsibility of the parent, and of the community, for manipulating a child's development – the socialization and education, that predestine him to function as a particular kind of human being?

These questions are properly applied to the destinies of particular individuals born day by day. Gloomy predictions about the long-range future of the species might be substantiated as a side effect of medical care and other welfare measures that avert the pain of natural selection. However, the pace of discovery in genetics is so rapid compared with that of biological evolution that we can afford to wait another fifty or a hundred years before we tackle the species problem. We will then have sharper tools, and at least as much wisdom about how to use them. Meanwhile we have enough to do in trying to minimize the enormous burden of personal distress and anxiety that attends our genetic load as it is manifest birth by birth, death by death.

Table 1. Potential technologies of eugenics and euphenics

A. *Selective mating*

- (1) By phenotype of parents (assisted by biochemical and cytological assay)
 - (a) negative – distracting, discouraging or sterilizing the 'unfit';
 - (b) positive
 - (i) encouraging select pairs,
 - (ii) with artificial insemination, donor ('rational germinal choice'),
 - (iii) with oval or ovarian transplant,
 - (iv) both, or fertilization in vitro, followed by implantation,
 - (v) extracorporeal gestation (test tube baby) – see also euphenics (i–v are not very different in their *genetic* consequences).
- (2) By genotype of parents – as above, with deeper analysis of parental constitution. Except for specific aberrations very little can be said at present about genetics of *desirable* traits.
- (3) By relationship of parents
 - (a) inbreeding. The main impact is to expose recessive, usually deleterious genes; increase phenotypic variability of F_1 ; decrease the genotypic variability of later generations;
 - (b) outbreeding – antithesis of (a). Most cultures strongly encourage outbreeding.
- (4) By age of parents – to forfend accumulation of deleterious mutations and chromosome anomalies which increase with parental age.
- (5) By phenotype or genotype of the zygote or of fetus (antenatal diagnosis and voluntary abortion). Earlier selections would avoid the trauma of aborting an established fetus.

- (6) By genotype of the gametes, e.g. separation of X from Y, or normal from defect-bearing sperm.
- (7) With sperm of other species (compare 1b iv). Nothing is known of the consequences among primate species. All contemporary races of man appear to be freely interfertile.

B. *Innovations in zygote biology*

Vegetative (asexual) propagation. Cloning.

- (1) Parthenogenesis – development of an unfertilized egg. (This might be genetically identical to the mother, or might be a product of meiosis, which would be an intense form of inbreeding).
- (2) Regeneration – development of whole individual from somatic tissues (as in some plants and lower animals like earthworms).
- (3) Differentiation of gametes from somatic tissues previously subject to extensive genetic manipulation.
- (4) Somatic reduction in gamete-forming cells in culture (somatic inbreeding) – would allow predictable outcome of further matings from a given parent which is not now assured.
- (5) Nuclear transplantation – renucleation of a fertilized, enucleated egg. Genetically equivalent to cloning from the source of the nucleus.
- (6) Embryo-splitting to produce twins or multiples. Not to be confused with multiple ovulation (occasionally induced by fertility-promoting drugs). About one third of spontaneous twins are monozygotic, i.e. arise from the splitting of one embryo. Note also the opposite phenomenon.
- (7) Embryo fusion (chimerism) so that one individual comprises two or more genotypes. This grades into tissue transplantation at later stages. It should allow different genotypes a new latitude for mutual complementation, e.g. *mens sana in corpore sano*. Somewhat less than one thousandth live births are spontaneous chimeras, but some of these arise by other mechanisms.

C. *Adjuncts from somatic cell biology*

For eugenic applications these would be coupled with procedures like B (5). For euphenic effects, altered cells can be grafted back to a host or some manipulations done directly on his tissues.

- (1) Algeny – directed alterations of genes
 - (a) controversial claims of effects of DNA uptake in mammalian cells following a long tradition of genetic work with DNA in bacteria;
 - (b) incorporation of viruses
 - (i) experimental tumor viruses,
 - (ii) use of specially modified viruses,
 - (α) vaccination to induce immunity to viruses,
 - (β) virogenic therapy to replace missing genes,
 - (γ) virogenic enhancement for superior performance – if we but knew the biochemistry thereof;
 - (c) specifically induced mutations. No plausible approaches are now apparent.
 - (2) Random mutation and specific selection of cells with altered properties has full precedent in strain selection in microbes. Many uncertainties relating to possible cancer potential of such implants.
 - (3) Cell fusion to form somatic hybrids. These cells may then lose various chromosomes to give many new forms. Extends scope of (2). Can be readily applied to fuse *cells* from 'distant' species, e.g. fish and human.

- (4) Development of symbiotic strains of lower species, with habitats that grade from the external world (e.g. crops) to internal, to intracellular. Parasitic worms in man have evolved in this direction with the help of adaptations to thwart immunological rejection. In principle they might be domesticated. So also might algae be trained to an intracellular habitat in man where they might photosynthesize essential nutrients, if not bulk calories, as they already do in primitive animals.

References

1. BRIGGS, R., KING, T.J.: Transplantation of Living Nuclei from Blastula Cells into Enucleated Frog Eggs. *Proc. nat. Acad. Sci. (Wash.)* 38, 455-463 (1952).
2. GURDON, J.B.: Transplanted Nuclei and Cell Differentiation. *Science* 219, 24-36 (1968).
3. SHOCKLEY, W.: Is Quality of U.S. Population Declining?, interview; in: *U.S. News and World Report*, 22. 11. 1965.
4. SHOCKLEY, W.: A 'Try Simplest Cases' Approach to the Heredity-Poverty-Crime Problem. *Proc. nat. Acad. Sci. (Wash.)* 57, 1767-1774 (1967).

Further reading

- ARON, R.: *Progress and Disillusion*. New York: Praeger, 1967.
- CARTER, C.O.: Genetics of Common Disorders. *Brit. med. Bull.* 25, 25-57 (1969).
- DAVIS, B.D.: Prospects for Genetic Intervention in Man. *Science* 170, 1279-1283 (1970).
- HANDLER, P.: *Biology and the Future of Man*. Oxford: University Press, 1970.
- LEDERBERG, J.: Orthobiosis: the Perfection of Man; in: *The Place of Value in a World of Facts*. (Nobel Symposium XIV.) New York: Wiley (interscience), 1970. This Nobel Symposium XIV paper includes a comprehensive bibliography.

Summary

Advances in molecular biology promise to enlarge our technical capacity to intervene in genetic problems. Social and ethical factors are therefore likely to play an increasingly important role in determining the application of new scientific advances in man. This is no cause for great alarm, for the same principle already applies to the use of surgery and of other medical interventions that could, in theory, also be applied for extraordinary 'renovations' of human nature.

The evolution of wise policies for the use of genetic advances, and the surveillance of existing practices for compliance with consensual ethical standards, and for the anticipation of social injury, of course requires a widely disseminated understanding of the probable potentialities of various types of genetic intervention.

The most important influences on the genetic composition of the human species are likely to remain side effects of other global policies: the movement of populations, transportation technology, the effects of war and of discrepancies in economic development and attention to welfare, and the level of education and understanding of reproductive processes.

Geneticists can help to bypass difficult moral problems involved in the calculated reduction of the genetic load from deleterious genes by encouraging

more effective attention to preventive genetic hygiene, especially through the identification and elimination of principal environmental sources of gene mutation.

Specific options for genetic therapy include the rapidly developing field of antenatal diagnosis (coupled with elective abortion of threatened fetuses); cell and organ transplantation; and virogenic therapy. The latter would entail the introduction of desired DNA segments into domesticated strains of viruses; these would then serve for the vaccination of patients lacking a critical metabolic function, which would then be restored under the influence of the added DNA.

The renucleation of eggs (cloning) is also a theoretical possibility, likely to be of more metaphorical than pragmatic interest. The discussion of cloning may help to illuminate the ethical problem of parenthood, generally: what is the responsibility of each generation for the biological and educational predetermination of its successors?

In any event, the central responsibility of the geneticist qua physician is to the welfare of his individual patients.

Zusammenfassung

Fortschritte in der Molekularbiologie bieten gute Aussichten für vermehrte technische Möglichkeiten, in genetische Probleme einzugreifen. Soziale und ethische Faktoren werden daher eine zunehmend wichtigere Rolle bei Entscheidungen über den Einsatz neuer wissenschaftlicher Erkenntnisse beim Menschen spielen. Das ist kein Grund zu übertriebener Sorge, da das gleiche Prinzip bereits für die Anwendung chirurgischer und anderer medizinischer Maßnahmen gilt und sich theoretisch auch zu ungewöhnlichen «Renovationen» der menschlichen Natur verwenden ließe.

Die Entwicklung wohldurchdachter Grundsätze für die Anwendung genetischer Fortschritte, für die Überprüfung bereits bestehender Verfahren in bezug auf ihre Vereinbarkeit mit den allgemeinverbindlichen ethischen Grundsätzen und zur Verhütung sozialer Ungerechtigkeit erfordert natürlich ein stark verbreitetes Verständnis der wahrscheinlichen Auswirkungen verschiedenartiger genetischer Eingriffe.

Die wichtigsten Einflüsse auf die genetische Zusammensetzung der menschlichen Spezies werden vermutlich auch in Zukunft die Auswirkungen anderer weltweiter politischer Entwicklungen haben: Bevölkerungsbewegung, Transparttechnologie, Folgen von Krieg und von Diskrepanzen im wirtschaftlichen Wachstum und in der Fürsorge, im Bildungsniveau und im Verständnis der Fortpflanzungsmechanismen.

Die Genetiker können helfen, schwierige moralische Probleme im Zusammenhang mit der gezielten Reduktion der durch schädliche Gene entstehenden erblichen Belastung zu umgehen, indem sie der vorbeugenden genetischen Hygiene größere Aufmerksamkeit zuteil werden lassen, besonders durch das

Erkennen und das Beseitigen primärer umweltbedingter Ursachen von Genmutationen.

Spezifische Anwendungsmöglichkeiten für eine genetische Therapie bieten unter anderem das sich rasch entwickelnde Gebiet der pränatalen Diagnostik (kombiniert mit elektivem Abort gefährdeter Feten), die Zell- und die Organtransplantation sowie die virogene Therapie. Die letzterwähnte Methode würde in der Einführung gewünschter DNS-Segmente in domestizierte Virusstämme bestehen, die zur Impfung von Patienten benutzt werden könnten, denen eine kritische Stoffwechselfunktion fehlt und die dank dem Einfluß der zugesetzten DNS wiederhergestellt würde.

Eine weitere theoretische Möglichkeit, die allerdings vermutlich von eher symbolischem als pragmatischem Interesse ist, bietet die Renukulation oder das «Cloning» von Eizellen. Die Erörterung des Cloning-Verfahrens mag helfen, das ethische Problem der Elternschaft in einem umfassenden Sinne zu beleuchten: welche Verantwortung trägt jede Generation für die biologische und die bildungsmäßige Prädeterminierung ihrer Nachkommenschaft?

In jedem Falle besteht die wichtigste Pflicht des Genetikers als Arzt darin, auf das Wohlergehen jedes einzelnen seiner Patienten bedacht zu sein.

Résumé

Les progrès de la biologie moléculaire promettent d'accroître les moyens techniques dont nous disposerons pour tenter de résoudre les problèmes génétiques. C'est pourquoi les facteurs sociaux et éthiques joueront probablement un rôle de plus en plus déterminant pour l'application à l'homme des nouvelles réalisations de la science. Il ne faut pas voir là de grands motifs de s'inquiéter, car le même principe intervient déjà en chirurgie ainsi que dans toutes les autres formes d'intervention médicale qui pourraient en théorie être aussi mises en œuvre pour «rénover» de façon extraordinaire la nature humaine.

Mettre au point des lignes directrices prudentes applicables aux progrès de la génétique, surveiller les méthodes actuelles pour s'assurer qu'elles sont conformes au consensus éthique en vigueur et qu'elles ne porteront pas, à longue échéance, tort à la société – autant de mesures qui exigent, bien sûr, qu'un public très étendu comprenne les possibilités qu'offrent les différentes formes d'intervention génétique.

Il est probable que les influences principales qui s'exerceront sur le patrimoine génétique de l'espèce humaine ne seront jamais que des sous-produits d'autres politiques d'application plus générale: mouvements de population, technologie des transports, conséquences des conflits armés et des disparités du développement économique, souci du bien-être social, niveau d'éducation et compréhension des processus de la reproduction.

Les généticiens peuvent contribuer à la solution des problèmes moraux difficiles à résoudre qui interviennent lorsqu'il s'agit de réduire de façon calculée le

nombre des gènes nuisibles dans le profil génétique de l'homme en encourageant l'application d'une hygiène génétique préventive plus efficace, moyennant en particulier la détermination et l'élimination des principales sources écologiques des mutations génétiques.

Parmi les options précises de la génétothérapie, nous mentionnerons le domaine en évolution rapide du diagnostic prénatal (associé avec l'avortement volontaire des fœtus génétiquement menacés), les greffes cellulaires et organiques et la virogénétothérapie. Cette dernière méthode pourrait comporter l'introduction de certaines fractions sélectionnées d'ADN dans des souches virales acclimatées qui serviraient ensuite à vacciner les patients à la fonction métabolique déficiente, qui serait ainsi rétablie sous l'influence de l'ADN apporté de l'extérieur.

La renucléation des œufs (clonage) constitue aussi une possibilité théorique qui présente probablement un intérêt plus abstrait que pratique. Le débat consacré au clonage contribuera peut-être à éclairer le problème éthique de la procréation dans un contexte plus général, en d'autres termes le problème de savoir dans quelle mesure chaque génération assume la responsabilité de la prédétermination biologique et pédagogique des générations qui lui succéderont.

En tout état de cause, la responsabilité fondamentale du généticien en sa qualité de médecin est de travailler au bien-être de chacun de ses patients.

Resumen

Es de suponer que los progresos de la biología molecular nos proporcionarán nuevas posibilidades técnicas de intervenir en los problemas genéticos. Por consiguiente, es probable que los factores sociales y éticos desempeñen un papel cada vez más determinante en la aplicación al hombre de los nuevos adelantos científicos. Esto no debe alarmarnos demasiado, pues lo mismo vale ya para la cirugía y otras formas de intervención médica que también podrían, teóricamente, llevarse a cabo para realizar extraordinarias «renovaciones» de la naturaleza humana.

La adopción de una línea de conducta adecuada que rija la aplicación de los adelantos en el campo de la genética, así como la vigilancia de las técnicas disponibles, al objeto de garantizar su conformidad con las normas éticas de la sociedad en que vivimos e impedir cualquier abuso social, requiere naturalmente un amplio conocimiento de las posibilidades que entrañan las distintas formas de intervención genética.

Es probable que las mayores influencias que se ejercerán sobre la constitución genética de la especie humana sigan proviniendo de otras decisiones de mayor alcance, como son: los movimientos demográficos, la mecanización de los medios de comunicación, las consecuencias de los conflictos armados y de

las discrepancias del desarrollo económico y del bienestar social, así como el nivel de educación y la comprensión de los procesos de la reproducción.

Los investigadores en genética pueden ayudar a soslayar los espinosos problemas morales que implica la corrección de defectos mediante reducción de los genes mutables, haciendo que se conceda más importancia a una higiene genética preventiva, especialmente determinando y eliminando las principales causas ecológicas responsables de mutaciones genéticas.

Entre las opciones precisas de la «geneticoterapia» cabe señalar el diagnóstico prenatal (inclusive el aborto provocado de fetos genéticamente amenazados), campo que está tomando gran incremento; el trasplante de células y órganos; finalmente, la terapéutica virogenética. Este último método supone la introducción de segmentos seleccionados de ADN en cepas cultivadas de virus, las cuales servirían posteriormente para vacunar a pacientes que carezcan de una función metabólica importante, para restablecerla mediante el aporte externo de ADN.

La renucleación de un óvulo (*cloning*) constituye otra posibilidad que presenta un interés más teórico que práctico. La polémica suscitada por el «cloning» quizás contribuya a elucidar el problema ético de la paternidad en un contexto más general: ¿Hasta qué punto ha de asumir cada generación la responsabilidad de la predeterminación biológica y formativa de las que le seguirán? De todos modos, la primera obligación del especialista en genética, en su calidad de médico, es la de velar por el bienestar de cada uno de sus pacientes.