BIO-ENGINEERING: MEDICAL DIMENSIONS

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Biology has been progressing at a rapid pace during the last forty years, particularly after the introduction of the methods of physics and chemistry in the study of living organisms. Up to a few years ago, this progress did not have dramatic effects on medicine. Today, however, we are seeing that the progress in cell and molecular biology has not only increased our understanding of many physiological and disease processes but is affecting the traditional way of practising medicine. The biological techniques that have special relevance to medicine include:

a. Cell culturing.
b. The use of restriction endonucleases which permitted the development of the recombinant DNA technology, gene cloning and gene isolation. Of particular interest for medicine is the preparation of "gene probes", that is, of specific DNA pieces (either isolated directly from the human genome or chemically synthesised), which are chemically altered to carry a reporter atom or molecule. With these probes it is possible to detect and localise specific genes, normal or abnormal, present on the human genome.
c. The production of monoclonal antibodies.

The combined use of these new techniques has many applications in medicine. Of these applications I will review briefly only those which pose new problems for the practice of medicine. In particular:

A. The production of human biological substances by recombinant DNA techniques like:

1. Hormones, growth factors, blood proteins, lymphokines etc. There are already on the market human hormones produced by these techniques.
2. Vaccines
3. Enzymes
4. Monoclonal antibodies for preparative, diagnostic and therapeutic use. This area of application of the new biological techniques opens up new possibilities for medicine. It does not, however, directly create new ethical problems.

B. Gene replacement

Modern techniques allow the isolation of practically any gene for which we can isolate the protein encoded by it. We can then introduce the isolated gene into a cell where it can function. The use of this technique can be either for replacement of a defective gene (therapeutic use) or for the introduction of a desirable gene (eugenic or euphonic use). We can distinguish two cases: In the first the target cell may be any somatic cell of an individual. Although gene replacement in somatic cells has not yet been achieved successfully in humans, there are reasons to believe that this will be accomplished soon. Despite the excitement that this novel therapeutic approach has caused, I believe that, from the ethical point of view, gene replacement is no different from any organ transplantation or even blood transfusion. It is a procedure that concerns only the particular patient in whom it is attempted. However, gene replacement in germ or embryonic cells is a completely different matter. The introduction of new genes into these cells may have an irreversible character since we may not be able to control the propagation of these genes once introduced into the gene pool of the population. It is for this reason that experiments of this nature are not allowed in humans (e.g. Warnock report in UK). Such experiments have already been attempted successfully in animals (transgenetic animals).

C. In-vitro fertilisation

Our ability to achieve the fertilisation of a human egg in vitro has opened up a whole new era of human biology. This procedure, in combination with other biological techniques, makes possible:

1. The freezing and storing of embryos.
2. Cloning of early embryonic cells. The early cells that derive from the division of the fertilised ovum each maintain the potential to produce a whole organism. So it is possible to use these cells either for the development of genetically identical individuals (like identical twins) or storing them for future use etc.
3. Research on early human embryogenesis. Our knowledge of human development is rather scarce. The possibility of studying human

development in vitro might provide important insight into the causes of congenital malformations or disturbances of normal differentiation leading to malignancies.

4. Use of embryonic cells for transplantation for the treatment of patients. There is a current heated debate as to whether it is ethical to use human embryos for research at all. The Warnock commission in the UK has recommended that an embryo of the human species should have a special status and that research on in vitro embryos should only be permitted up to 14 days after fertilisation. It is interesting that while we are very sensitive in protecting the rights of human embryos which are products of in-vitro fertilisation, at the same time, many countries have legalised abortion at will until a much lager stage of fetal development. Deciding whether to allow research on embryos is very difficult. The easy decision to forbid such research carries the price of much human suffering because of the delay in acquiring the necessary knowledge to ameliorate abnormal conditions like congenital malformations and malignancies.

D. Diagnosis of Hereditary diseases

The use of gene probes allows the detection of abnormal genes present in the genome of an individual. A new strategy based on so called "restriction fragment length polymorphisms (RFLP's)" allows the detection of genes responsible for a hereditary disease even if we do not know the precise cause of the disease or the exact location of the relevant gene on the chromosomes. Up to now we have been able to detect a number of abnormal genes but the list increases almost daily. We are becoming increasingly capable of "reading the DNA of the human genome". This ability to read the DNA may be used prenatally for the diagnosis of an abnormal fetus - "prenatal diagnosis" or post-natally, for the detection of the presence of an abnormal gene in an individual - "genetic screening".

1. Prenatal diagnosis
   The use of the term "diagnosis" in this case lies outside the traditional use of the term. The purpose of diagnosis in medicine is to assist in the treatment of the patient. Up to now, prenatal diagnosis, when positive, leads to therapeutic abortion i.e. the destruction of the patient. So this poses a problem from the start. But this problem is not a new one created by the new biology. Until the introduction of recombinant DNA technology, prenatal diagnosis was performed by biosying the relevant tissue from the fetus, a procedure which could not usually be performed before the 16-19th week of gestation. With techniques allowing the detection of abnormal genes by "DNA reading" i.e. before these genes are expressed, prenatal diagnosis can be done by chronic villi sampling, a procedure performed at the 8th-9th week of gestation, thus making termination of pregnancy much easier. It seems probable that in the future, prenatal diagnosis will be performed on fetal cells collected from the circulating blood of the mother, thus eliminating the need of embryo sampling by invasive procedures.
   Prenatal diagnosis by "DNA reading" is already being done and accepted for severe "early-onset" monogenic genetic diseases. That is, for diseases caused by the presence of a single abnormal gene with 100% penetrance, and which are manifested in early childhood e.g. thalassemia, sickle-cell anemia, hemophilia. But now we are about to extend the use of "DNA reading" in cases of "late-onset" genetic diseases i.e. severe diseases which manifest themselves relatively late in life, e.g. Huntington's chorea, a debilitating disease at the fourth or fifth decade of life. And here the question arises: Do we have the right to terminate the pregnancy of a fetus at risk for developing Huntington's chorea? Or to take a more extreme case, for Alzheimer's disease, a form fo senile dementia appearing at the 7th or 7th decade of life?
   But apart from the diseases characterised as genetic, that is for diseases caused by the presence of an abnormal gene regardless of other factors, there are a lot of diseases, including many of the most common, which are not genetic in the strict sense but for which there is a genetic "redisposition". This means that the genetic make-up of a person increases the risk of developing a particular disease, like heart disease, diabetes, certain forms of cancer etc. It is very probable that soon we will be able to detect the presence of these predisposing abnormal genes in the DNA of either a fetus or an adult person. Will the presence of a gene doubling, for example, the risk of an early heart attack be a sufficient reason to terminate the pregnancy of such a fetus?
   The ever increasing list of conditions for which prenatal diagnosis becomes possible, in combination with techniques making easier the sampling of early fetal cells, may have many consequences: they might push us to the slippery road of "perfection" making the indications for prenatal diagnosis and therapeutic abortion too broad, they might also make us put less effort and research into the treatment of these diseases since it will be easier to avoid bringing persons suffering from these diseases into life; and, furthermore, they might lessen the social responsibility for caring for these patients.
   I would like, at this point, to stress that the characterisation of a human gene as "normal" or "abnormal" has meaning only in relation to a particular environment in which the gene operates. And since humans shape their environment culturally, many of the genes considered abnormal today, may fall "within normal range" in the future because of cultural changes, the way the loss of the human genes for hairiness is not considered abnormal today.
2. The possibility of detecting susceptibility and making early diagnosis for genetic diseases before they are clinically manifested in adults (genetic screening) poses problems more immediate than prenatal diagnosis. Up to now the results of genetic screening have been used to counsel the affected individuals about martial and reproductive choices. But soon, occupational restrictions might be instituted for genetic reasons. For example, it has been suggested already that workers with alpha-1 antitrypsin deficiency, which predisposes to lung disease, should be excluded from jobs exposing them to asbestos. Exclusion of workers sensitive to a particular toxic condition might be preferred to providing healthy working conditions since it is cheaper. A more extreme case is the use of genetic information from occupational restrictions not because of increased job-related risks but even because of job-unrelated risks e.g. an employee may be excluded from a high level position because of his increased risk for early death from a heart attack.

Because of these potential problems some trade unions and other pressure groups have criticised the introduction of such testing as infringing on individual rights. I believe that proper use of such knowledge about our genetic potentials and limitations can increase our chances for a satisfying life and make us avoid activities for which we are not genetically endowed. However, these possibilities of easy "DNA reading" create problems of confidentiality and invasion of privacy which we will have to face. Our ability to read and directly manipulate our own genetic material as well as that of other living organisms poses questions we have not faced in the past. Not that genetic manipulation is something new. Since the dawn of civilisation, people have used it to their benefit: the domestication of wild plants and animals by selective breeding are cases of such manipulations. But these planned manipulations made indirect use of natural processes and did not concern humans.

The introduction of the recombinant DNA technology has mad possible direct genetic manipulations and the new power has created a lot of anxiety and fears. Some of these fears proved unfounded. For example, there was a lot of discussion and fear about crossing natural species-barriers, fear based on biological arguments. But we realised that species-barriers exist naturally in order to avoid inefficient matings leading to organisms unable to survive rather than to super-organisms able to take over the world.

The new biology provides us with unprecedented powers but is not devoid of dangers. We have to proceed with caution. Scientists have the obligation to inform the public concerning the scientific progress. We have the prospect of acquiring supremacy over the forces that have shaped us but are we wise and clever enough to know the long range consequences of our intervention?

Professor **George M. Maniatis** obtained his M.D. and Med.Sci. from the University of Athens Medical School, and a Ph.D. in biochemistry from M.I.T. A former Rector of the University of Patras and visiting Professor to M.I.T., he is presently the President of the Hellenic Society for Human Genetics, and Professor and Director of Biology at the University of Patras Medical School. He is a recipient of the "Medical Foundation Fellow", and the "J.T. Hirschl Career Scientist" awards.