The Future of the Gene: How Will the New Technologies of Molecular Genetics Influence Our Concept of Life?

Ulrich Pfeffer
Molecular Biologist, National Cancer Research Institute, Genoa, Italy

The advancement of the biological sciences in the last 30 years has led to a rapid increase in our knowledge on the molecular base of life and to the design of techniques to modify biomolecules including the genetic material. This advancement was possible due to the interaction of knowledge and technology since in molecular biology, the insight into the molecular mechanisms directly translates into the design of new tools, most often constituted by the newly discovered biomolecules themselves: living organisms provide the tools needed to modify them. Knowledge translates into application, which in turn promotes the gaining of knowledge. The orientation to potential application is thus naturally inherent in the biological sciences. This leads to a continuously growing path of development that makes the technological dominance of the living world conceivable.

The enormous complexity of life, on the other hand, determines a relatively slow translation of the knowledge into applications outside the laboratory. This often leads to unreasonable expectations, frequently spread by the scientists themselves. There is no article on biotechnology that does not claim the possible cure for nearly all known diseases although very few biotechnological drugs have yet come to the market. Many widely held believes in 'rationale drug design' have to struggle with complex and often unpredictable biological responses. Everybody knows that genetic manipulation will help curing genetically determined diseases yet this has so far been obtained only in very few experimental protocols.

If one would have predicted in 1960 that within 50 years from then, nearly every household in the developed world will possess a computer one would have been laughed at. If one would have predicted only 15 years ago that nearly everybody will have a mobile telephone probably the same would have happened. But we can say that we will cure cancer, AIDS and diabetes and that we will abolish the hunger in developing countries by gene transfer and nobody is laughing. Current biotechnologies are at the primordia and, for now, as smart in performance as computers in the sixties of the last century. Despite the breath-taking path of development it will take still a long time before the promises made can be fulfilled. The entire biotech industry is fueled by these expectations, but they also create an enormous pressure to translate the discoveries into products and hence to apply them.

New products, also new biotech products, have to be accepted by the market. Acceptance is challenged in two ways: i) by a generally less optimistic view of the technological future ever since the public discussion of nuclear power plants and ii) by a profound skepticism towards technologies that modify the living world, especially humankind itself. Manipulation of the genetic material evokes the resistance of a naive naturalism that would like to spare out living beings from the technological attack. Probably everybody of us feels that there must be limits to the genetic intervention at least as far as man is concerned. But this feeling than collides with the wish to cure people form various diseases or to avoid the birth of children with hereditary diseases who will experience a short life of tremendous suffering. There are conditions where very few of us would hesitate to advise the intervention to avoid the lives to come but the line that has to be drawn between acceptable and unacceptable diagnostic and therapeutic...
interventions is by no means clear. Nature itself does not supply a key for the interpretation. Guidelines for genetic diagnosis and therapy are decisions that must be taken by the society. They will be determined by the political, ideological, moral and religious orientations of those who participate in taking these decisions. The ethical issues raised by biotechnologies must be discussed on a very wide base. Bioethics cannot be left to institutionalized committees neither to the scientist themselves. The society as a whole must express its opinion free from the pressure to transform expensive investments into profitable products but free also from irrational fundamentalism.

Many tremendous diseases will hopefully be curable in not to far a future and in many instances, biotechnology will contribute to this goal. For most cases the way of how genetic manipulation can contribute to a cure is only hypothetical yet often the theoretic chance of cure is used to justify ethically controversial techniques or applications. Just like nobody in the scientific community would accept the sacrifice of a single person even if this could prevent the death from disease of a million others also any potential beneficial application does not constitute a priori a legitimization for a procedure or a product of life science technologies.

We focus in this issue on applications of biotechnology to the human genome in terms of genetic diagnosis and genetic modification. Genetic diagnosis can be performed on adults in the attempt to predict the individual's risk to develop certain diseases or, for the sake of reproduction, to predict the probability to conceive a child carrying deleterious genetic traits. Genetic diagnosis can also be performed on material derived from the fetus and, in the case of in vitro fertilization where the embryos undergo the first cellular division in the test tube, on single embryonic cells. Prenatal diagnosis or pre-implantation diagnosis helps to single out those who carry undesired genetic traits. The resulting decision is abortion or elimination (non-implantation) of embryos, respectively. At present prenatal diagnosis is mainly restricted to the analysis of chromosomal abnormalities, mostly trisomy of chromosome 21 known to determine the Down-syndrome. In future, as our knowledge on the genetic basis of diseases will grow, it will be possible to apply the approach to many other analyses. The technique itself will probably develop to be feasible earlier during pregnancy and to be less invasive.

Genetic testing of adults raises many ethical issues, many of which related to the genetic information: Who is entitled to know the test results and which use can be made of the information? Certainly, everyone has the right to know what ever he wants on the condition of his own genes. But genetic testing for genes that are related to susceptibility to disease is considered ethical only if prevention or therapy is possible. This principle leaves, however, space to interpretation for example in the case of the breast cancer susceptibility gene BRCA-1. Female carriers of this gene face a high risk to develop the disease at some time during life but at present there is no specific prevention available unless one considers bilateral mastectomy an option (1).

It is also generally accepted that genetic information may not be used for discrimination of any kind. Discrimination could for example occur when genetic information would be used in the selection of personnel, but is it ethical not to screen for genotypes that expose to a specific risk at a given workplace? Using the example already cited, should women carrying a mutated BRCA-1 allele work in radiology, considering the fact that the gene is involved in the repair of damage caused by radiation that, if not repaired, can lead to breast cancer? What is unethical in the example cited: the discrimination on the base of genetic information or unemployment that forces people into jobs that are deleterious to their health?

It is also widely held that insurance companies should not be allowed to ask for genetic testing. But what, if only the subscribers of insurance policies are informed on their personal risk to develop certain diseases? Can an insurance company work when only those who know to be at risk subscribe?
Genetic testing of the unborn raises different concerns: It is performed with the intention to avoid certain hereditary diseases. But most health problems occurring in the newborn, including very severe ones, are not determined by genetic defects but by other, environmental pre- and perinatal conditions. The decision to procreate entails the risk to have offspring affected by various kinds of diseases and malformations, of which only very few can be avoided by genetic testing. Once on the way deciding which genetic condition merits to be passed on and which must be eliminated, where will we find the line that separates healthy from ill or malformed? Imagine a world where in vitro fertilization and pre-implantation genetic testing is combined: many embryos could be generated and tested before the one 'acceptable' is found. Why should one accept in a world of this kind an embryo that has high risk to die from cancer, to develop Alzheimer's disease late in life, to be genetically obese or devoid of any musical talent? Normality, a concept that has been harshly criticized in psychiatry is not less problematic in biology. Very few genetic conditions are really independent from the environment. People affected by phenylketonuria, a potentially fatal mono-genetic disease, can happily live just observing a diet devoid of phenylalanine, carriers of trisomy 21 (Down-syndrome) conduct a serene live when appropriate assistance is guaranteed. Moreover, our very limited knowledge on gene function does not allow to rule out the possibility that an allele that determines a disease might also determine specific characteristics of the carrier that he or she would enjoy. Who can exclude that Alzheimer patients benefit from particular intellectual or emotional features that positively contribute to their personality before they actually develop the disease late in life? Most probably Mozart suffered from Tourette's syndrome, a neurological condition that has often been associated to musical talent. Should we have aborted Mozart? Considering our ignorance on gene function, how can we exclude that together with the disease a precious part of genetic diversity will be destroyed?

Who at the end takes these decisions? The edition of a list of 'permitted' and 'forbidden' alleles by the legislator is unconceivable, so the decision lies by the future mothers and fathers. But on which base do they decide? Will they follow trends and fashions in their decision? Do parents decide today to abort a Down-syndrome fetus just fearing the others asking: 'Didn't you get the testing done?'.

Probably only few ethic controversies will arise concerning somatic gene-therapy. Gene-transfer to cells that cannot transmit this modification to future generations raises concern with regard to the safety of the treatment among which the necessary guarantee that the transgene is not taken up by germinal cells or spread to other persons. On the contrary, the intervention on the cells that transmit the altered gene to the next generations is considered unethical. But for many it is unethical because it is unsafe. When safer technologies become available the issue of germline manipulation will be back on the agenda. But most probably, even safe technologies will be feasible only for the manipulation of one gene at a time. Yet the application to monogenetic diseases makes not much sense since the carriers of mutated alleles can easily be identified by genetic diagnosis and can abstain from procreation. But if two carriers of the same gene defect desire a child nonetheless, the diagnosis must be done on the fetus creating ethical concern related to prenatal diagnosis. The intervention on the germline could thus be considered a way to avoid ethical problems with prenatal diagnosis and genetically guided abortion: put out the fire with gasoline?

Diseases caused by a single gene defect are very rare. Most diseases develop by an interaction of genes with the environment (soil and seed). The gene effect is further reduced by the ability of man to modify the environment so as to dampen the deleterious consequences of gene defects. Moreover, genes interact which each other and we are yet beginning to understand some of these interactions. The dogma one gene-one protein-one function has been abandoned even by the toughest reductionists, but there is still a widely hold believe that each gene has one main...
function exerted with a certain independence from the genetic and environmental context. Yet laboratory mice tell another story: genetic manipulation is done on mice that have been crossed many times to yield a genetically homogenous group to be studied. But these mice are not genetically identical. Many genetic manipulations such as homologous recombination where a specific gene of the mouse is disrupted or mutated lead to different phenotypes in the offspring of the manipulated founder. The degree to which a genetic trait becomes manifest in the phenotype is called 'penetrance'. For many, perhaps the majority of genes analyzed, penetrance is not complete even within a genetically homogenous group. If such animals are crossed to other strains the phenotype often varies from not evident to severe. Reduced penetrance (in a laboratory setting of homogenous environment) indicates that there are other genes that in some way influence the function of the gene analyzed. Most probably, the number of genes that really act alone is very, very low. Most genes interact with many other genes which on their own behalf can be present in the population in many functionally different forms (alleles) and the consequence of a mutation depends on the alleles to which it is combined in a given individual.

As a result the effect of a mutation is not predictable with certainty. If one takes into account that the effect of most genes on the phenotype also depends on the environment in terms of pre-, peri- and postnatal conditions, the best description of the gene effect approaches some kind of principle of indetermination. This, in addition to technical and ethical problems, determines tight conceptual limitations to reasonable genetic manipulation. The genes contained in a genome form a network of transversal rather than hierarchical functional interactions as a consequence of casual mutation and selection for fitness during evolution. A mutation in a gene normally serving in a specific cellular function will be fixed by selection even if it affects a formerly completely unconnected cellular pathway as long as it determines enhanced fitness. The evolution of the genetic network and the genome as a functional unit are still confined in a conceptual limbo, simply due to the impossibility to approach the issue with the present technological means. The question rises whether the conceptual limitation should determine a corresponding limitation to applications.

Genetic diagnosis and therapy or more generally, imaginable future applications of our knowledge and technologies to man raise many other ethical problems that are not addressed here. What is our biotechnological horror vision? Ethical concern, especially in Europe, is heavily influenced by the experience of Nazi-fascism in the last century. The fascist utopia of the perfect race with its misconception of genetics has led to the holocaust. Today we are concerned of a capillary technocratic dominance over the whole life including the biological base of individuality. Genetic diversity just like socio-cultural diversity is freedom; there is no such thing like genetic perfection. But is thise authoritative implementation of eugenics still a realistic fear? Perhaps modern society creates new risks of abuse of technological means that have nothing to do with the creation of semi-intelligent workers or warriors or with the physical extinction of people belonging to ethnical groups. Perhaps a free market where free individuals select which genes should be present in their offspring and which not is a more realistic concern: Will there be free consumers that desire to avoid the psychological burden of genetically determined obesity for their children? Will we ask our grand-sons and daughters whether they have taken a look at the genetic profile of their partners before they decide to marry? Will genetic 'health', longevity, and beauty become a privilege of the rich in the developed world?

Modern democracy must limit the rules that interfere with the free decision of the individual to those aspects where undeniable rights of others or of the society as a whole are touched. The law must tolerate technological applications if they are desired and do not harm anybody else. The legal positions of the embryo who is touched by the decision on genetically determined abortion and of future generations who are touched by the manipulation of the germinal cells present particular problems. Most societies have found a compromise between the rights of the unborn and the rights of the woman who carries it. The compromise between the right to manipulate
ones own genome and the right to inherit a "safe", unmanipulated genome is to be found, if germline manipulation should ever be considered legal.

Apart from legality, everybody is free to limit its own actions to what he or she personally believes ethically correct. If we are free to do we are also free not to do. With this issue we hope to contribute to the process of finding a bioethical consensus for a future where the genome will not anymore be inviolable.

Note

(1) No specific prevention means that the prevention normally advisable for all women does also apply to carriers of BRCA-1 mutations. Preventive screenings such as breast self examination and mammography are to be initiated earlier during life in mutation carriers. Diet and physical exercise are considered to have a potential influence on the breast cancer risk in general. Women who are aware of a mutation might thus observe the prevention rule with particular attention. But the same could be obtained advising generally all women, not only the mutation carriers in breast cancer risk families to follow these strategies. This would have the additional benefit that also those in a breast cancer family who do not carry the mutation would stick with particular attention to the prevention that is beneficial regardless of the mutational state.

(2) The wish to be biologically father or mother can be very strong, but in general, modern society does not pay much attention to the transmission of the genes to future generations. Many couples decide not to have children at all or have just one. This is in contrast to the recent explosion of technologies of assisted fertilization that help people who are unable to have children of their own. Either the wish to have biological children is greater in people that are biologically impeded to have them (a psychologically intriguing hypothesis) or the technologies are insistently offered once the impediment is diagnosed (an ethically detrimental practice). As a consequence, much of the problem could be overcome without technology. The impelling wish of a child that carries their genes brings the potential parents into close neighborhood of genetic reductionists since they share the concept of genetic determinism. Otherwise they would opt for adoption. Another explanation is that bureaucracy hinders adoption. As a solution it seems reasonable to liberalize adoption rather than to apply fertilization technologies.

(3) The inverse relation is also true: there are very few diseases that are entirely environment borne. Alcoholism may help to explain this: Uncontrolled drinking leads to several diseases among which liver cirrhosis. This appears to be a disease that is exclusively determined by the environment but probably many genes determine which quantity of alcohol you need in order to destroy your liver. As a matter of fact, women need much less than men and sex is genetically determined.

(4) In consideration of this, the scientific journal "Molecular and Cellular Biology" has created a rubric where gene disruption that does not lead to an altered phenotype can be published.