Ethical and Legal Aspects

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All living structures have a genome, which contains the "blueprint" that provides all the instructions necessary to make and maintain an organism. With the exception of the red blood cells, each of the various billions of cells which make up each individual, contains a complete genome.This consists of a double chain of deoxyribonucleic acid (DNA). The chromosomes are portions of DNA plus protein. Our genes, ca. 100,000, are a small part of the very long stretch of DNA which is composed of about 3 x 10 nucleotides, generally abbreviated as "bases". These bases contain the purines, adenine and guanine and the pyrimidines, cytosine and thymine. The double chain is so formed that whenever there is an adenine in a chain, there will be a thymine in the opposite chain and whenever there is a guanine in one there will be a cytosine in the other chain. A great portion, ca. 90%, of the nuclear DNA does not contain genes. On the other hand the very small DNA of the mitochondria is occupied entirely by genes, and is inherited entirely from the mother. This has a very important application in legal medicine as will be extensively covered in this encounter. In this regard, because of its historical interest I will refer to the work of Mary Clare King with the children of the Grandmothers of the Plaza de Mayo in Argentina. Also, I will discuss the Declarations of Valencia and of Bilbao. Because of its pioneer interest, the 2nd Declaration of Valencia is included.

All our DNA is subject to continuous changes, i.e. mutations, by a wide variety of agents. There are many mechanisms to correct mutations. It should be noted that the mutation rate is from 10 to 100 times higher in mitochondrial DNA than in nuclear DNA and that the mitochondria are not as well endowed to correct mutations as is the nuclear DNA. Indeed, because of this it has been suggested that aging is related to the higher mutation rate of mitochondria. In many cases mutations are not corrected in which case they may affect a gene or result in an extensive modification of the DNA, e.g. excessive multiple repeat copies of trinucleotides will give origen to a disease; these repetitions tend to increase in successive generations and thus the severity and frequency of the disease.

In a somewhat arbitrary way we can divide the medical applications resulting from the increased knowledge of the Human Genome into diagnostic and therapeutic. The latter could be divided into "direct" (gene therapy) and into "indirect" (gene oriented pharmacology). Of course the new predictive medicine, including genetic counseling should be included here.

Because of its novelty a major portion of this resume will be devoted to gene therapy and to brief considerations of ethic and legal issues.

The term human gene therapy came into use because it identified, as presumptively beneficent, technologies that might have provoked more opposition if called human genetic engineering. Particularly in the 1970s, when any development or means for altering the genetic capacity of

human cells was hotly debated and bitterly opposed by some; the question, if asked, "What are the good uses of human genetic engineering? might have produced a negative response. Human gene therapy is and sounds benign.

On September 14th of 1990 a little girl four years old, with a deficiency of adenosine deaminase (ADA), was injected with millions of her own T cells in which had been inserted a normal ADA gene. This was done in the Childrens Unit of Intensive Care of the Clinical Center of the National Institutes of Health (NIH) in Bethesda, Maryland. That was the beginning of gene therapy in humans. Although gene therapy is a rational and logical treatment for certain types of diseases in humans, until rather recently the use of this type of technology was criticized as something very far in the future and almost science fiction. As a consequence, there was very extensive debate before the protocol for ADA deficiency was approved. Nevertheless, once it was shown to be possible, most people were favorably impressed. Thus, in spite of the few people who suffer from ADA deficiency in the whole world, the protocols used to correct this deficiency played a key role in the demonstration of the feasibility of gene therapy, and therefore established the first step towards a new Medicine. The Advisory Committee of the NIH (RAC) has approved some 90 protocols for several diseases, whereas the first gene therapy protocol of Anderson (1989) for ADA was reviewed 15 times by 7 different regulatory bodies. A mere six years later most protocols can be approved on a standard FDA review. Also Great Britain, France, Italy, Holland and China have started to use some 50 protocols in quite a number of patients, as of September of 1995. Interestingly the majority, 80%, are for cancer, or cancer related protocols.

This is not surprising since, indeed, it has become evident in the last two years that in addition to the approximatly 4000 monogenetic diseases known, potentially all diseases have a genetic origen. That is to say that many diseases have a polygenic origen, for example a large portion of persons affected with diabetes, and that the predisposition to a number of diseases also has a genetic basis. In all likelihood, a great deal of emphasis in the future will be given to treat the more common diseases, and precisely by their being more common they will be of more interest to society and thus to industry. This will have great benefits for many people including those of the 3rd World, but may carry the paradoxical danger of postponing or forgetting the treatment of certain monogenic deseases, particularly the less common ones, although these were the ones which originated gene therapy!.
Although the advances in Gene Therapy are impressive, it is necessary to advance much more, particularly in gene transference; it is also necessary to insure that treatments are not reserved for a few privileged persons or as a show for a few top hospitals. Ideally, there should be a great deal of emphasis in making possible the use of injection of genes, to avoid the need for large multidisciplinary groups as is the case now. There is a need to be able to integrate specific genes in the cell genome of the recipient so as to eliminate the risk, even if low, of initiating a cancer in the treated individual due to the possible integration of the new gene near an oncogene or near a gene dealing with tumor suppression. There is a need to regulate the expression of the new genes, particularly for the future and in the treatment of diseases such as diabetes in which the deficient genes necessitate a precise regulation. For the immediate future, gene therapy will be restricted to the treatment of somatic cells and it is unlikely that it will be extended soon to germinal cells. However, there will doubtless be much debate as soon as someone submits a protocol for germinal cells, since obviously any gene modification of these cells will be transmitted to future generations.

Although, gene therapy does not resemble any form of treatment previously used in medicine, it has, as any other experimental approach in medicine, the same restrictions based on ethical,

scientific and safety principles. As in any treatment, we should make sure that the balance, risk-benefit, will be toward or in favor of the patient. Finally, society must have access to the facts related to protocols. The absolute clarity of information given to the public is the best guarantee of social responsibility and of the concern of the scientific community.

In short any major Scientific advance or program often generates new dilemmas. The notable advances in the Human Genome Project have without doubt presented new problems and brought back to light older ones. There is no doubt that public enthusiasm is great, but it is mixed with the fear of how the new knowledge will be used. The discussions about how new genetic knowledge is going to concern us all will increase in the coming years. Principles of bioethics elaborated recently in relation to people, benefits, autonomy and justice, must be included in legal protection of the people as well as of society. These principles will not be adequate to solve many of the complex questions and controversies resulting the advances in genetics. Certainly, ethical dilemmas will arise because of the conflicts between collective and individual interests.

So-called eugenics and racial hygiene were based on an erroneous belief in the improvement of the inheritance pool, leading to negation of individual decisions about having children, choosing mates, and, under nazi genocide, the right to life. Eugenics in terms of coercive social politics has not disappeared; it is alive in some countries in which there are still sterilization codes, and as ideology it is taken into consideration in some countries and is trying to appear in certain groups, e.g. American right-wing extremists. Investigations related to behavioral genetics and their results are easily misused, as we have often seen in the controversies about IQ tests, affective disorders and other mental diseases. The problems and dilemmas related to the use of eugenic information will not need special draconian measures, but we must be ready. For example, employers, personnel directors and insurance companies could discriminate against those whose genetic characteristics make them susceptible to certain diseases, premature death or disability. Without doubt there is a potential conflict between individual interest and those of society. However, no one chooses his or her genes, and the information given by them must be kept confidential. No one should be analyzed genetically without his knowledge, and the information obtained must not be released without the consent of its owner, unless it is necessary to avoid damage to other people.

The human genome project will increase and present new problems. For example if a genomic analysis can predict that a person will die still young of a serious genetic disease, which until now is without treatment; would anyone like to be analysed?. There are already examples of persons who do not want to know, and have the right not to know. What would be their attitude if he/she knows that such an analysis can imform them whether or not he will pass such a disease to his descendants. There will be more rapid developments of genetic probes to detect diseases than cures for such diseases!. Will the increased knowledge of the Human Genome increase the tolerance of society toward persons affected by disease or will it increase discrimination?. Present laws offer some protection but would they be able to cope in a just and reasonable way with the new information revealed by the increased knowledge of the human genome?.

II WORKSHOP ON INTERNATIONAL COOPERATION FOR THE HUMAN GENOME PROJECT: ETHICS. Valencia declaration on ethics and the Human Genome Project.

1.- We, the participants in the Valencia Workshop, affirm that a civilized society entails respect for human diversity, including genetic variations. We acknowledge our responsability

to help ensure that genetic information is used to enhance the dignity of the individual, that all persons in need have access to genetic services, and that genetics programs abide by the ethical principles of respect for persons, beneficence, and justice.

2.- We believe that knowledge gained from mapping and sequencing the human genome will have great benefit for human health and wellbeing. We endorse international colaboration for genome research and urge the widest possible participation of countries throughout the world, within the resources and interests of each country.

3.- We urge coordination among nations and across disciplines in the conduct of research and the sharing of information and materials relating to the genomes of human beings and other organisms.

4.- Concerns about the use and misuse of new genetic knowledge have provoked debate in many quarters. In addition to discussions in professional circles, further public debate on the ethical, social, and legal implications of clinical, commercial, and other uses of genetic information is urgently needed.

5.- We support efforts to educate the public, through all means including the press and the schools, about genome mapping and sequencing, genetic diseases, and genetic services.

6.- In light of the great increase in prognostic and therapeutic information that will arise from the genome project, we urge greater support for training of genetic counselors and genetic education of other health professionals.

7.- As a general principle, genetic information about an individual should be ascertained or disclosed only with authorization from the individual or his or her legal representative. Any exceptions to this principle require strong ethical and legal justification.

8.- We agree that somatic cell gene therapy may be used for the treatment of specific human diseases. Germ-line gene therapy faces technical obstacles and does not command ethical consensus. we endorse further discussion of the technical, medical, and social issues on this topic.