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Human Genome Project: Ethics



OBJECTIVE

It has become increasingly important to improve international agreements. Although in Science there has traditionally been informal cooperation, it has been carried out by a few or by small groups of scientists interested in specific problems. Only more recently some larger groups have been organized and supported by a number of nations; hopefully there will be more in the future. The new prominent role of biology in many countries with its benefits, especially medical and technological, requires generous and efficient mechanisms to benefit other less scientifically prominent countries as well as support from private and governmental sources for projects which because of cost and/or worldwide interest make cooperation desirable if not essential. The recent interest and debate regarding the Genome Project, especially as it applies to humans, indicate the necessity for international programs. This workshop had as its main aim to stimulate international cooperation in the ethical aspects of the Human Genome Project. We thank the many participants who contributed their time and talent in the realization of this aim.



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Human Genome Project: Ethics

This volume contains the papers offered at the II Workshop on International Co-operation for the Human Genome Project, organized and sponsored by the Banco Bilbao Vizcaya Foundation in collaboration with the Valencian Foundation for Advanced Studies.

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Human Genome Project: Ethics

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PRESENTATION

It is today possible to trace out a genetic map, to offer a description of a complete biological book of the human being. Yet this scientific knowledge can be used in diverse ways.

Responsible procedure demands that the scientist should foresee as far as possible the consequences to be derived from the applications of these advances in the understanding of living matter. Profound ethical dilemmas are posed by the new possibilities open to us.

The BBV Foundation, in its concern to create spaces for thought that help to point to ways of solving these problems, takes upon itself the task of providing the means to do just this.

Reflecting competently and authoritatively on the ethical implications of the human genome will perhaps not lead to an elimination of the uncertainties which the Human Genome Project will bring mankind over the next few years. However, it will enable us to prepare advantageously for confrontation with these uncertainties as to the conditions in which our behaviour evolves in new environments against new options and alternatives.

Our Foundation is proud to have sponsored and collaborated in the organization of this important workshop, in which some of the greatest world experts have had the occasion to inform us and match their own conclusions with those of their colleagues. I should here like to express my sincere thanks to all of them and particularly to Prof. Santiago Grisolía.

We hope that this publication, which offers in sufficient detail the interventions of the 36 experts who participated in the II Workshop on International Co-Operation for the Human Genome Project: Ethics, in the city of Valencia, may thus become a useful reference guide both for scholars and specialists in this field and for those who in some way are responsible for managing and orienting the activities and patterns of behaviour of their fellows.

José Angel Sánchez Asiaín

President of the Banco Bilbao Vizcaya Foundation.

INTRODUCTION

Santiago Grisolía

Institute of Cytological Research, Valencia (Spain).

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Institute of Cytological Research, Valencia (Spain)

Since this conference is concerned with international aspects of cooperation on ethical issues in Human Genome research, I should like to begin by pointing out that it is generally accepted that the Human Genome Project and programmes associated with it are likely to present society with a number of important ethical and social problems, as well as the benefits, in the decades to come. Scientists thus have a responsibility to inform other sectors of the community, and the decision makers in particular, of their advances and the new dilemmas. The 1988 workshop held in Valencia, to which I shall refer later on, marked an important first step in the interdisciplinary debates that will be needed.

I proposed therefore to Dr. José A. Sánchez-Asiaín, president of the Banco Bilbao-Vizcaya Foundation (FBBV), approximately one year ago, that a meeting be held focused the ethical aspects of the Human Genome Project. I would like here to thank Dr. Sánchez-Asiaín, and the board of the FBBV, for accepting that proposal and for sponsoring this meeting, which, without doubt, has been very successful.

These words have to be considered as a simple introduction to this monograph which contains many of the excellent contributions of the participants in this meeting which should interest many.

A most important goal of science, or better said, for the scien tist, is to make public his discoveries and thus share his knowledge but without the opportunity to claim priority, scientists would lose what is probably the most attractive incentive for their work; that is, the admiration and/or envy of their colleagues, as well as demonstrating the importance of their work to the society which supports them. This is now more important than ever since not only the Genome Project but much of modern science requires ever more and greater resources and support from the society.

To whom do scientific discoveries belong? In earlier times, when scientists received help and subsidies from private patrons or foundations, their proprietary interest could be defended. In biology major discoveries have often been made without asking for financial benefits. We have the examples of the penicillin discovery from which neither Fleming, Florey nor Chain derived any fiscal benefits, or more recently the discovery of monoclonal antibodies by Kohler and Milstein. Things have changed dramatically in recent times, however with the massive support that science needs and receives from society. Thus, and although up to now the american as well as other Governments have been lenient and have in fact encouraged the free patenting of new biological discoveries and even species, we must come to a clear decision for the inmediate future regarding the Human Genome initiative.

If we accept that the Human Genome is a patrimony of mankind, the situation and the answer is clear. There should be a complete,

rapid and frank disclosure. However, the scientist of the present generation, and I daresay of all, have made a fetish, as I have already indicated, of claiming priority. Thus the situation becomes more complicated and difficult.

This workshop has been very important because under the present structures and customs, I see no easy way whereby total sharing of the project can be reached on a widespread, if not completely international level, *unless we insist and work very hard* to change habits and suspicions on the creation and sharing of knowledge. This sharing may be reached mainly in the ethical and social aspects. Remember, however, that ethics as such is not an objective discipline. Rather it tends more to employ principles that vary with time and people.

As we pointed out by Robert Cook-Deegan, who worked tirelessly on and during the programme, the second workshop tried to clearly analyze and integrate the social implications of work on the Genome as it relates to research and the investigators in this area.

Without going into detail, as already mentioned, ethics represents and reflects the customs accepted by a society. Now the almost exponential development of science and its impact on society modifies and will, without doubt, continue to modify ethical concepts, as was pointed out in the first workshop held in 1988. After that workshop the urgent need to devote time to the ethical aspects of the project through an interdisciplinary meeting became even more apparent, since man is able to, and must, anticipate events and possible consequences of his acts.

A strong influence leading to the establishment of this interdisciplinary meeting was the concern expressed by many that biomedical investigators might encounter the same problems suffered by nuclear physicists after World War II. Many investigators who worked on nuclear fission, and therefore with the atomic bomb, manifested afterwards their regret at having participated and, above all, resented the imposed commitment to secrecy which denied them frank and open discussion of their work. Another important reason for the workshop was the historical fact that there were some scientists in the past who developed and conducted programmes in eugenics. This has darkened genetic research and is a factor leading some countries and certain groups to fear genetic research.

Certainly there are serious doubts about leaving human genetics in the hands of a scientific elite. Such fears ares especially strong in Germany, as has been stated by many, although many more have actually had it in mind. Someone has said –I believe it was the astronomer Hoyle, and I hope he was joking– that in a few years we will see the nuclear physicists free and the genetic investigators behind bars.

The last decade has been especially notable in the development of techniques and advances in molecular biology and genetics, culminating during the last five years in the proposal of the feasibility of the project known as the Human Genome Project. The idea, which was proposed independently and almost simultaneously by several US scientist, developed into national research programmes in many countries besides the USA, such as Italy, the UK, the USSR, Japan, and France. Without doubt, other nations will join and also create their own national programmes.

I would like to stress what the current minister of education, Javier Solana, told me some time ago, that Spain should participate in the Genome Project, although little has been done thus far to develop it. Until now, the ministry in Spain which has shown more interest is that of health and its competent minister, Julián García-Vargas, who aided and attended also the first workshop and then kindly arranged for me to participate with him in a long interview with the president of the government, Felipe González. The president showed a resolute interest in the active participation of Spain in international collaboration and in the feasibility of developing a national programme. Mr. González showed a broad knowledge of the social and ethical problems entailed as a result of the advances in the Human Genome Project. This is why I am trying to ascertain the potential and number of young spanish investigators who are interested and may be able to develop a programme similar to those of other countries and perhaps one or two centres devoted to the Human Genome Project. With this aim, we will in the course of 1991 assemble those spanish scientists who would like to participate, to study the feasibility and then make recommendations for the development of a mobilizing programme. It is also hoped that the example of Spain will stimulate others and give recognition to the fact that certain international organizations, especially UNESCO, are giving their moral and as much material support as possible to advance the still unexplored genetic frontiers, with the hopes, first of being able to combat diseases more efficiently than in the past, and second of knowing each other better.

There is no doubt that public enthusiasm is great, but, as already mentioned, it is tinged 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 include in legal protection of the people as well as of society. These principles, among which the Declaration of Valencia must be considered pioneering, will no be adequate to solve many of the complex questions and controversies resulting from this step forward 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 even at present 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. As we have mentioned before, 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 among individual interests and those of society. However, we should remind the reader that no one chooses his or her genes, and that the information given by them must be 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. All these aspects were discussed during this second workshop, which originated the II Declaration of Valencia.

We were aware that this workshop could not solve many ethical problems, because they encompass more than the scientific basis. But investigators have a very important role, I daresay, today more than ever; they must express and publicly discuss their work. Fortunately they have been the first in recognizing the importance of such questions and are aware that their findings can be misused. Thus, they are in a perhaps less than enviable position to originate public debate about these new areas. I have said that public powers and organizations cannot ignore them, but they must be prompted to defend and modify their priorities.

I repeat, it is necessary to have clear explanations and extensive discussions. The II workshop on international cooperation for the Human Genome Project: Ethics, was a pioneering event in assembling an interdisciplinary group of outstanding leaders in genetics, clinical research, social science, theology, humanity and government.

I believe it would be a waste not to use as a basis for future implementation the resume of Valencia, the conclusions of which were reached after a spirited discussion led by Drs. Wyngaarden and McKusick. It is noteworthy that although there was a vigorous case made for UNESCO's cooperation, the name of this agency did not appear in the Declaration of Valencia due to the larger influence and novelty I believe, of the then newly formed

Human Genome Organization (HUGO). From my viewpoint, this was a serious mistake, particulary since UNESCO has a broad network as well as administrative know-how. In this regard, and as I pointed out in a report of the Hastigns Center (July/August, 1989), a number of comments were heard at the time of the first meeting in Valencia suggesting that if the then newly formed HUGO organization were to be effective, each nation, including the small nations, must contribute to the funding according to their possibilities.

In resume, I suggest that cooperation at an international level is difficult but necessary and reachable with different degrees of early success depending on continous and vigorous expositions and discussions such as the ones which were developed during this workshop.

WORKSHOP ON INTERNATIONAL COOPERATION FOR THE HUMAN GENOME PROJECT. Valencia Declaration on the Human Genome Project

1. The members of the workshop believe that knowledge gained from mapping and sequencing the Human Genome can have great benefit for human health and wellbeing. Towards these ends, participating scientists acknowledge their responsibility to help ensure that genetic information be used only to enhance the dignity of the individual. They also encourage public debate on ethical, social, legal, and commercial implications of the use of genetic information.

2. The members endorse the concept of international collaboration for the project and urge the widest possible participation of countries throughout the world, within the resources and interests of each country.

3. The participants strongly encourage parallel studies of genomes of selected animal, plant and micro-organism models in order to achieve a deeper understanding of the Human Genome.

4. The workshop urges coordination of research and information on complex genomes among nations and across disciplines and species.

5. The workshop believes that information resulting from mapping and sequencing of the Human Genome should be in the public domain and made freely available to scientists of all countries.

6. The participants encourage continued effort to develop compatible genomic data bases and networks and measures to ensure world-wide access to these resources.

7. The workshop endorses The Human Genome Organization (HUGO) as the lead body, in collaboration with other non-governmental and government organizations, to promote the goals and objectives addressed in this declaration.

October 24-26, 1988
Valencia (Spain)

WORKSHOP ON INTERNATIONAL COOPERATION FOR THE HUMAN GENOME PROJECT. Valencia Declaration on the Human Genome Project

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October 24-25, 1988
Valencia (Spain)

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 responsibility 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 collaboration 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, though 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.

November 14, 1990
Valencia (Spain)

GENERAL REMARKS

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GENETIC POLYMORPHISM AND THE SURROUNDING ENVIRONMENT

James Watson

Cold Spring Harbor Laboratory, New York (USA)

ABSTRACT

The genetic differences observed between people, which are the basis of human evolution, are both important and frequent, and determine the existence from serious illnesses to skills and aptitudes typical of man. However, it is very difficult to show how much is genetic determinism and how much is environmental inheritance.

It is equally difficult to find an answer to the question of how to deal with this human genetic variability.

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It is equally difficult to find an answer to the question of how to deal with this human genetic variability.

We owe a great deal of gratitude to Santiago Grisolía for bringing us together to discuss the ethical implications of the Human Genome Project. The Human Genome Project has an extraordinarily important objective: to work out the complete set of instructions which make us human, as distinct from say a monkey. It is a difficult question, however, to probe how much we are determined by our genes as opposed to our environment. Moreover, even given the sum of our genetic and environmental heritages, I don't think there is anyone here in this room who feels that in some sense or other he or she doesn't have free will. In any case, we go about our lives acting as if we are not constantly held back by our genes.

That we all do not have the same set of genes is obvious. Genetic analysis only can exist if you observe differences between two individuals, and it was by observing the distribution of traits passed down from parents to progeny that Mendel's laws were worked out. The question thus becomes, are these differences in humans major or minor? Many people would like to wish these differences to be minor, and that all human beings are born with virtually equal chances to succeed in their later lives. As scientists, however, we know these latter longings do not reflect reality. Major genetic differences abound and are seen in their most extreme forms in individuals suffering from horrid genetic diseases like muscular dystrophy or Tay-Sachs disease.

These all too many such forms of genetic injustice arise through throws of the genetic dice that operate when our sperm and egg are formed. This genetic variability between humans reflects the fact that the gene duplication process is not perfect, and the new genetic mutations are constantly arising. There is no way to stop this process. Moreover, this variation has been the basis of our evolution. Without the differential survival of more fit variants, we as human beings would not have our high powered brains that have let us develop the languages, both spoken and written that underlie the creation of our various civilizations.

The question now faces us, as we work out the details of the human genetic message, as to how we are going to deal with these differences between individuals. In the past, at the time of the Eugenics movement in the United States and in England, and during the reign of racist thoughts in Nazi Germany, there was very little genetic knowledge. Most decisions then were made without solid genetic evidence. There were many prejudices, but almost no real human genetics. Now we have to face the fact that we soon will have real facts, and how are we going to respond to them? Who is going to take care of those people who are disabled by the genes they have inherited? How can we compensate them for the fact that many individuals are not as equal genetically as other people? I don't think we know the answers, and that is why we are here for this meeting.

THE HUMAN GENOME PROJECT AND PUBLIC OPINION

Jack McConnell

Hilton Head Island, S.C. (USA)

ABSTRACT

Bearing in mind the rapid political-economic changes that have taken place on a world-wide scale over the last decades, with growing emergency of the subject, the author proposes that before continuing with the Human Genome Project, and in order to avoid future rejection of the project by public opinion, this programme should be presented to society, including the ethical considerations it entails.

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We are gathered here to begin three days of intense examination of the ethics issues of the Program to Map and Sequence the Human Genome. I wish it were under different circumstances. I would like the world to be less turbulent, would be easier to measure the effects on society of our work. But that is not the case. Our program is just getting underway at a time when the world is in the midst of its greatest period of transition in a century or more. In simpler times changes occurred but we had time to reflect on the changes and adapt to them. Not so now. The dominant theme of the next few decades is the increasing rate and pace of change occurring. It is true not only in the scientific arena but in all sectors of society.

National barriers, which have stood defiantly for decades, have come turbling down in a matter of months. Commercial barriers have disappeared among some of the world's great economies, resulting in the development of new markets. International competition is emerging from some of the most unexpected places reversing the roles of suppliers and consumers. World powers, who until recently faced each other through gun sights, now find common ground in trying to roll back aggression of others. I have listed only a few of the areas affected but, in truth, no sector is spared.

While the world is doing it's own topsy tervy dance, we are engaged in the development of technology which may, in the long run, create more change than any of the global events now underway. They shuffle money, power, markets and politics. Our activity holds the potential to change man at his most fundamental level. With this in mind it is imperative that we pause in our program and come to gripe with the ethical issues inherent in our efforts.

For centuries the scientific community has been able to operate with a high degree of autonomy and independence. We have been able to select and pursue our own areas of interest, answering to very few. With the transitions occurring in society, has come a new awareness by the public that they want to be more involved in scientific initiatives. They want not only to be informed of the results of our efforts but to be involved in the plannig and execution as well. They may not understand the scientific terms but they have a solid intuitive feeling regarding the ethical issues involved and how they will impact them.

Unless and until we are fully equipped and prepared to take into account their anxieties and concerns and to present our program to them, including especial our views of the ethical issues, they may delay or call a halt to our efforts. It has happened before and could easily happen again.

The format of the conference has been developed to provide for an intense examination of the ethical issues, and we hope that

occurs. Whether or not the conference is a success depends on you. Your insights, vision, input of energy and your will can make this a great conference.

This is as unique opportunity for the program to map and sequence the Human Genome, for the scientific community and for society. Whether or not the conference is a success depends on you. The input of your vision, energy, insights and will can make this a great conference.

Now let it begin and when we finish may be able to say we have served well. The Program, the scientific community and society.

SCIENTIFIC REVISION

SCIENTIFIC REVISION

THE CURRENT STATE AND FUTURE PROSPECTS OF THE PHYSICAL MAPPING OF THE HUMAN GENOME

David Schlessinger

Department of Molecular Microbiology and Centre of Genetics in Medicine, Faculty of Medicine of the University of Washington, St. Louis, MO (USA)

ABSTRACT

The construction of a Human Genetic map is a feasible aim thanks to the availability of new technologies. In this sense, large-scale cloning methods, amongst which the artificial methods produced by yeasts (YAC) are the most highly developed, provide intact genes which facilitate the integration of broad contiguous fragments. In this way, easy, rapid coverage of large regions of the genome is achieved. The analysis of the YAC's, as likewise other alternative techniques, shows the effort required to attain wide-ranging mapping.

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ABSTRACT

The construction of a Human Genetic map is a fascinating challenge to the availability of new technologies. In this sense, large-scale cloning methods, amongst which the artificial methods produced by yeasts (YAC) are the most highly developed, provide intact pieces which facilitate the integration of broad contiguous fragments. In this way, easy, rapid coverage of large regions of the genome is achieved. The analysis of the YAC's, as likewise other alternative techniques, shows the effort required to attain wide-ranging mapping.

At the time when the Human Genome Initiative stimulated discussions of optimistic 5 or 10-year targets for complete analysis of genomes, both the physical mapping and sequencing that were implied aroused skepticism among many workers in the field. In the intervening years, the mapping goals and even some of the sequencing goals have become much more tractable. The reason is clear: the availability of new technology.

The nature of the map remains the same in all formulations. Maps are characterized by a number of properties, the chief ones being continuity and resolution. For complex genomes, the goal is clearly to obtain long-range contiguity of DNA and, eventually, to extend analyses until the total sequence of the DNA is available. In other words, complete continuity of the map would be achieved with maximum resolution to the nucleotide level.

Here I will concentrate mainly on the impact of yeast artificial chromosomes [and to a lesser extent, of polymerase chain reaction (PCR) methods] on large-scale cloning and DNA analysis for map construction. I will also discuss briefly the development of a number of potentially strong methods to build contigs and to approach closure of partially-formed maps. This leads to some final comments about the progressively increasing complementation of technologies –both for mapping and sequencing, and for genetic and physical mapping– that is making a unified map a feasible goal.

YACs as a cloning vector of choice

Regarding the optimal cloned unit for mapping purposes, it is now clear that large-scale cloning methods –of which yeast artificial chromosomes[1] are the most developed– can provide even quite large genes intact and in normal context for biochemical and genetic studies; and that such clones can facilitate the assembly of large contigs[2]. As a result, the unit of cloned DNA used as a building block in the assembly of contigs is clearly shifting decisively towards a yeast artificial chromosome. There are a number of reasons for this; but they include both *a priori* considerations and practical limitations of other methods.

Conventional cloning methods, for example, rarely exceed 40 kb in insert length. Furthermore, cosmids, lambdas, and other standard vectors have been shown to clone complex genomic DNA in a biased fashion, so that more than 10^4 holes might be expected in a cosmid library of Human Genomic DNA.

In contrast, YACs can be 20-fold the size of cosmids. Their large size means quicker and easier coverage of large genomic regions. Also, when the representation of genomic DNA in YACs is tested, it seems to include much if not all DNA cloned

in more-or-less random fashion. Data with YAC cloning of *D. melanogaster* and *C. elegans* DNA have generally been in accord with this view [3, 4]. For human DNA, a comparable inference can be made from at least three lines of evidence: first, YAC contigs of 2 Mb or larger have been assembled for a number of sites in the Human Genome (see, for examples, refs. 2, 5, 6, and 7); second, screening of a library of total human DNA in YACs with a series of several hundred probes found cognate YACs for nearly all of the probes tested (ref. 8 and Brownstein et al. unpublished results); and third, the yield of numbers of cognate YACs from a library of four genomic equivalents of Xq24-Xq28 YACs, in the studies of our laboratory with that of M. D'Urso (see below), has consistently been indistinguishable from the expectation by Poisson statistics –that is, every segment of human DNA seems to have a comparable chance to be cloned into YAC vectors [9]. Figure 1 emphasizes the contrast between YAC and conventional cloning systems schematically.

YACs are not an ideal cloning vector. For example, 1% of them are patently unstable, throwing off deletion derivatives during growth, and in current libraries, 10 to 30% of the clones contain disparate segments of DNA artifactually cocloned from different portions of the genome. However, the availability of many probes and of a number of YACs from any particular locus facilitates the identification and analysis of these artifactual clones –and once again, the frequency of scrambled clones in no greater than that observed in cosmid libraries. YACs thus have some deficiencies, but are the best thing available, and they continue to be improved.

The handling and analysis of YACs –like so many investigations of DNA– is greatly facilitated by the polymerase chain reaction, which permits the selective amplification of specific bits of cloned DNA, facilitates the diagnosis and comparison of mutated compared to normal DNA without the need to clone any of the sequences, and also permits easy recovery of probe and sequence information from cloned DNAs –such as from the ends of YACs [10, 11, 12].

The power of the combined use of YACs and PCR has encouraged the development of a format for maps that provides a common language for maps of all types. It is based on the use of "STS's" or sequence-tagged sites, primer pairs that define characteristic PCR products for corresponding points in the genome [13].

Approaches to contigs

Commitment to YACs as the primary clonig tactic does not, however, determine the selection of a strategy for mapping. In particular, there are two criteria that are especially important:

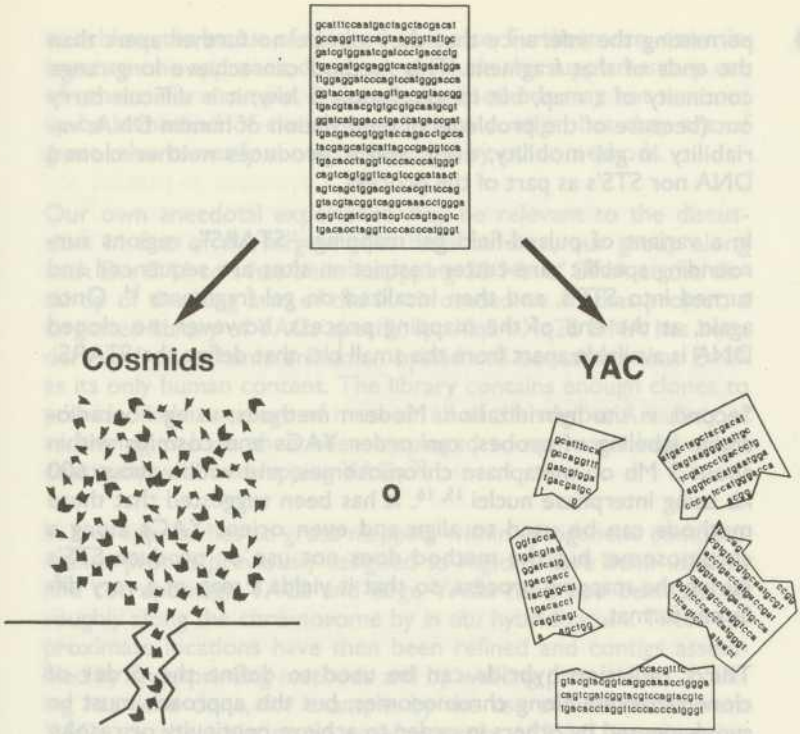


Figure 1. *The putative advantage of YACs and other large-fragment cloning methods.* The genome is shown as a "book", with an alphabet of the four different letters spelling out the long genetic message of 100,000 genes arrayed in a total 3,000,000,000 nucleotides. With conventional vectors, the genome is broken up as if it had been shredded, into pieces the size of a word or phrase. Also, a fraction sufficient to leave 10,000 holes in the total is unclonable and therefore lost from attempts to reconstruct the entire genome from fragments. In contrast, YACs are of the size of a paragraph or halfpage, and can clone most or all of the genome, facilitating the assembly of the entire genome in overlapping fragments (contigs).

First, does a map require that cloned DNA be available across its breadth? Some mapping methods, as indicated below, do not commit themselves to the provision of any substantial amount of cloned DNA. For medical and research purposes, however, it seems certain that workers will generally want to have cloned DNA at their disposition for further analysis.

Second, what is to be the format of the map? The STS formulation is widely favored by investigators and by the Genome Initiative Advisory Board in the United States; but it is by no means agreed to by all groups.

It may be useful to indicate some of the alternative formulations and technologies in the field at present.

First, pulsed-field gel mapping. In this method, probes are sought which will hybridize to the same large DNA fragment in a gel,

permitting the inference that they can be no further apart than the ends of that fragment. This method can achieve long-range continuity of a map, but its resolution is low; it is difficult carry out (because of the problems of methylation of human DNA; variability in gel mobility, etc.); and it produces neither cloned DNA nor STS's as part of the process.

In a variant of pulsed-field gel mapping, "STARS", regions surrounding specific rare-cutter restriction sites are sequenced and turned into STS's, and then localized on gel fragments [14]. Once again, at the end of the mapping process, however, no cloned DNA is available apart from the small bits that define the STARS.

Second, *in situ* hybridization. Modern methods, using nonradioactive labeling of probes, can order YACs and cosmids within about 3 Mb on metaphase chromosomes, and within about 600 kb using interphase nuclei [15, 16]. It has been suggested that these methods can be used to align and even orient YACs along a chromosome; but the method does not use or produce STS's during the mapping process, so that it yields a map of a very different format.

Third, radiation hybrids can be used to define the order of cloned markers along chromosomes; but this approach must be supplemented by others in order to achieve continuity or resolution. In one formulation, a set of radiation hybrids are used with auxiliary techniques to define the order of a number of probes; and the probes are then used to screen libraries for cognate YACs [17]; but it is not clear that such methods permit any real gain over strategies that rely directly on cycles of screening for YACs with random probes.

Fourth, identification of overlapping regions by fingerprinting of clones, a technique which has permitted the assembly of large contigs for *E. coli* [18], *S. cerevisiae* [19], and *C. elegans* [20], retains considerable power; but it is as yet unclear whether it can muster sufficient discrimination to permit the assembly of contigs across the vast stretches of much more complex genomes; and once again, in its pure form, it neither uses nor generates any STS's. An elegant formulation of one version of fingerprinting has been presented by Lehrach, employing the information derived by hybridization of a series of oligonucleotide probes to arrays of clones [21]

The tactics employed by different strategies can also vary considerably. For example, fingerprinting and *in situ* hybridization generally depend completely on hybridization methods, whereas other approaches employ more PCR-based technology.

At present, a healthy spirit of competition pervades the efforts at long-range mapping, and it will not be clear for some time which methods will be most efficient, inexpensive, and powerful enough

to achieve the status of method of choice. Furthermore, commitment to one approach does not preclude the supplementary use of others –for example, fingerprinting methods may not turn out to be a method of choice to generate contigs, but they are of great value to verify contigs assembled by other methods.

Our own anecdotal experience may be relevant to the discussion. In one of the largest pilot tests to date, our group along with Dr. D'Urso's has been mappping 50 Mb of DNA at the distal tip of the long arm of the X chromosome. In that project, a targetted library of YACs specific for Xq24-Xq28 DNA has been derived from a hamster/human hybrid cell containing that DNA as its only human content. The library contains enough clones to provide likely coverage of most or all of the region. A variety of technologies have then been employed to approach long-range contiguity with overlapping YACs [22].

In two approaches to gross mapping within cytogenetic compartments, probes previously assigned to regions have been used to find correpondign YACs and large YACs have also been placed roughly along the chromosome by *in situ* hybridization. These approximate locations have then been refined and contigs assembled by fingerprinting methods and by walking procedures. Walking has been done, for example, by the use of end-clones from YACs, by the isolation of end-fragments of YAC inserts using PCR-based methods, and by the use of a radioactively-labeled YAC as a probe against the entire collection. In this way, contigs of up to 4 Mb have been derived, and there seems to be no profound barrier to the reassembly of much of the region in overlapping YACs.

There have been two deficiencies in this work that have, however, increasingly concerned us. First, the work produced no STS's, so that long-range contiguity was achieved without the desired map format, requiring the addition of STS's as a detached exercise thereafter. Second, hybridization was used for the recognition of YACs, and has often produced false positives, based on cross-hybridization, and false negatives, based on poor growth, weak signals, etc. We have therefore turned in our own case to a different paradigm of map formation.

Overlapping YAC/STS content mapping

Philip Green has suggested a particularly promising way to assemble overlapping YACs and generate a map with the progressive accumulation of STS's, using a combination of traditional and PCR-based methods [23]. We have adopted his method, STS content mapping, for our current work. In this approach, probes and STS primer pairs are generated independent of the collection of YACs. Each primer pair is then used to find cognate YACs, each

of which is recognized because it produces the appropriate PCR product starting with the primers. Thus, scoring is absolute, and positives can be clearly distinguished. Furthermore, their common content of STS's progressively assembles YACs into contigs of overlapping DNA, In this way, the formation of the map and the accumulation of overlapping YACs proceeds in parallel, and map construction makes use of the discriminating power of PCR-STS methodology. This method is now in active use at the Center for Genetics in Medicine at our University.

The problem of closure and the promise of convergent technologies

"Closure" remains a special, important, and still very challenging area in mapping. It is still not clear whether YAC contigs –which are likely to be the most extensive contigs available for the fore seeable future– can truly be generate at the Mb level everywhere across chromosomes. Even if they can, they will presumably reach a limit size at points where DNA is either unclonable or unstable in YACs. And once contigs have reached limit size, the problem of fitting them together into a longer-range contiguous map (closure) remains. Fortunately, here as well, a number of methods can be reviewed which can order and orient contigs. They include both genetic techniques (linkage mapping) and physical mapping techniques such as in situ hybridization [15, 16] jumping libraries [24], pulsed-field gel electrophoresis [25], and radiation hybrid mapping [26].

It is especially notable in regard to closure that it is possible to develop mapping strategies that do double duty. Just as overlapping YACs can be found and a map can be simultaneously formatted using STS's, so the use of STS's that reveal polymorphism in the human population provides a way to refine the genetic map, to order contigs, and to merge the physical and genetic maps. Such approaches suggest that optimism about very extensive long-range mapping of complex genomes within the decade may not be misplaced.

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SEQUENCING THE HUMAN GENOME. CURRENT STATE

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ABSTRACT

The Human Genome Project really aims at identifying the ADN of organisms with genomes of very different dimensions. At present, the sequencing of ADN enables us to attack human illnesses, to fight ecological problems or study evolution. In future, molecular biology will be a theoretical biology and we shall know the genes we all have in common, as also those which are different in each individual.

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The DNA sequence of a genome gives us information about the genes of the organism. The goal of the genome project is to work out all the genes of the very simplest organisms, the more complicated ones that we study as models, and the genes of our own bodies. To do that requires that we work out the DNA of organisms whose genomes range in size from one megabase to 3,000 megabases. The smallest of these organisms may have 500 genes, a single eukaryotic cell like yeast may have 5,000, while we have something like 100,000 genes.

The DNA content of a human cell, written out in letters, would fill one thousand 1,000-page telephone books. We often speak of that DNA as containing or encoding 100,000 genes. In some ways that is a misstatement of the complexity, because we know that genes are commonly related and fall into families or superfamilies, each having of the order of 10 to 100 members. Therefore, this complexity is actually something of the order of 1,000 to a few thousand different gene structures. But many of the genes in our bodies are alternatively spliced. In the brain the most complicated protein that I know, N-CAM, has already at least 50 different splicing patterns. I think that when we look at the structure of our genes and ask what individual structures will do what different things, we will find about several million gene variants in the brain and of the order of 100,000 gene variants in the body. Thus, to understand the full complexity of the organism is going to be very difficult. How are we going to find out these details of structure, and specifically how the individual genes determine the individual parts of our bodies?

The answer is that we are going to do it by sequencing. Although we will identify a number of genes by mapping and other techniques, ultimately we are going to predict the majority of gene forms from their sequence.

I would like to say a word about sequencing. At the moment the DNA sequencing that we do in the laboratory is dominated by four elements, of almost equal difficulty. People often think that the effort of sequencing is dominated by running electrophoretic gels or doing chemistries. In fact, most of the effort is spent in preparing the DNA, much is spent in reading gels into the computer, and a great deal of effort is spent in composing the sequence in the computer. The automatic machines are essentially devices for reading the gels, and today there are a variety of computer approaches to solve this problem. The assembly of sequence is becoming well-defined. The process to the gels from the chemistries is straight forward, and the major effort, I think, that will simplify the bulk sequencing, will be in solving the first problem.

Over the next few years there are going to be a series of large sequencing projects. We are going to do one on mycoplasma. There are now three *E. coli* projects in the world. There is a *C.*

elegans project between England and America; there is a yeast project going on in America and a yeast project going on in Europe. Within this next period, the first large amounts of coherent DNA sequence will appear.

In America, the 1995 goals of the genome program, stated in a five-year plan, are to have sequenced 20 megabases of DNA from model organisms and to have sequenced approximately 10 megabases of human DNA, in large, coherent regions, and to have brought the cost of sequencing down to something like $0.50 per finished basepair. It is generally believed that the cost today of sequencing is of the order of $1 to $2 per finished basepair, based on estimating what the large, reasonably well-trained laboratories spend in terms of doing sequence.

My own expectation, now that I have given you the national goal, is that the world is going to change much more rapidly so that by 1995 the cost will fall to less than $0.25 a base and the first human chromosome will have been sequenced. By the year 2000 the cost will have fallen to something like a penny to a, few cents a base, and all the human chromosomes will have been sequenced.

How will this happen? As the world starts large sequencing projects in several laboratories, each will begin to do down the experience curve, the learning curve, and we will develop, as happens in every industrial production project, defined, simpler, and cheaper methods. Each increment in production by a factor of ten generally is associated with a drop in cost by a factor of two. The amount of sequence to be produced is such that the cost should drop over time to the levels that I have just suggested.

Furthermore, something else is happening in our science at this time that is generally unrealized. At the same moment that molecular biology has become the underlying science that pervades all of biology, it seems to be failing as a science! Today, not only do we attack problems of human disease, as we discussed this morning, by looking at genes and looking ad DNA sequences, but we attack problems of ecology by studying the DNA sequences of bacteria, we study problems of evolution by comparing the DNA sequences of different organisms, we study problems in structural cell biology by looking at the DNA sequences of components of the cell. Molecular biology, over the last five years, has penetrated all of biology by using its ability to isolate genes and work on their sequences. Yet at the same time, as we begin talking about a human genome project, then trying to work out all the genes of the organisms around us in the world, people are wondering, or complaining, or suggesting, that something is wrong with biology because everyone seems to be sequencing, and we all know that sequencing is boring. I think what is happening,

what we don't realize, is that we are going through a paradigm shift; our science is changing around us.

Today molecular biology is dominated by an experimental approach: we define a phenotype, we find a gene, we work out its sequence, we study a protein. We experiment first and think later. Tomorrow that will'no longer be true. Molecular biology will be dominated by theory: one will think of the properties of a gene and then go to do experiments. That is a shocking change.

Today molecular biology is dominated by techniques like libraries, cloning, sequencing, PCR reactions, yet all of these are becoming more and more conventional. They can all be looked up in a book, the Maniatis Cookbook, or purchased as kits, "follow the procedure in the insert".

All of these techniques will move from the laboratory into support facilities over the next few years. That has happened before in biology. In the 1970's, the restriction enzymes went from the forefront of research in the laboratory to being purchased. In 1960, one had to synthesize radioactive triphosphates in order to work on the biosynthesis of nucleic acids. Soon after that they could be purchased. It constantly happens in science that new elements which had been breakthroughs then became conventional things that one has technicians work out or one purchases from the stockroom. In the future, the genome sequences will be put in a database, and that database will be the major research tool. From those sequences we will predict first gene products, alternative splicing, and control sequences. Then we will predict the interactions of gene products, and finally we will predict the ways in which the genes form the organisms. Today, if we had the sequence, we could obviously predict families of genes, strutures of receptors, the regulation of transcription. Tomorrow I promise you a theoretical biology in which we first predict all aspects of gene interaction and then go to do experiments.

I said this paradigm shift is actually here. Today the database is large enough to begin to dominate molecular biology. The reason for this is that the amount of DNA sequence in the database has gone up 60% a year for the past 15 years. That is a factor of 10 every 5 years. Today there are 50 megabases of sequence in the database. (There are about 10,000 laboratories around the world working on some aspect of sequencing genes). Five years ago there were only five megabases of DNA sequence in the database, five years before that there were only 500,000 bases of DNA in the database. This is a dramatic change over time. If one works out the structure of a gene today, one's first question is to go to the computer to see if somebody has found something similar. About 70% of the time, somebody has, and if they haven't, you had better keep your eye on the computer because a week later

somebody else will have found some gene that is just like the one you have found.

What consequence does this rate of growth have for the future? Five years from now, if those rates continue, we will have 500 megabases of DNA in the database, and by the year 2000 five billion bases of DNA in the database. This projected rate of increase is essentially a restatement of the Human Genome program. If current trends continue, five years from now one expects to be doing chromosomes a year and by the end of the century genomes a year.

I think the world will go even further than that. Ten years later, by 2010, I expect that we will be able to sequence a million bases of DNA for $300. Sequencing whole genes will become a medical diagnostic. You will be able to examine a gene in your body completely. A few years after that, by 2020, I expect that you will be able to go to your corner drugstore, and for $300 you will be able to leave a blood sample and get a compact disc. That single compact disc will contain a Human Genome; your own. When we describe the human genome as a string of letters extending all around the world if written out using one centimeter for each base, it seems immense. In terms of the computer potentiality that we each have on our desks, the information in the genome is not that large.

I expect that we are going to know the genes that we all have in common, about 90% of our genes, by the end of the century, and we will know most of the variations, those 10,000 genes that differ across human beings within 10 to 20 years after that.

That is the problem that faces us. It is not really that we are doing a new project which will make this happen. We are at a point in our science where the march of knowledge is carrying us forward to the end that we will be able to embed ourselves, all of our genes, in the background of all living species in the world, and we will be able to trace the movement and creation of each of our genes throughout the entire course of evolution.

The purpose of this week is to discuss some of the effects of this jump in knowledge. One effect of this jump is a philosophical one. There will come a moment, sometime in the next five or ten years, when the world realizes that there is some truth in the statement that we can have a human being on a compact disc. That is going to be a philosophical shock to us and to the world because it reflects, in a high degree, the extent to which biological science defines, of fails to define, a human being. Humans often think of themselves today as having almost infinite potential. As scientists, of course, we have had to learn to live over the years with the fact that our bodies have a genetic dictation, that much of our structure and behavior is the product

of genes inherited from our parents. The world does not yet live with this realization. The world will have to fight off succumbing to a shallow genetic determinism, "my genes made me do it!" and also must find a balance between genes as structural determinants of the individual's body and brain and our ideas of mind, liberty, self-determination, and individual worth.

NATIONAL POLICIES

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THE HUMAN GENOME PROJECT. THE FRENCH VIEW

Jean François Girard

Direction Générale de la Santé. Ministère des Affaires Sociales et de la Solidarité, Paris (France)

ABSTRACT

The French Government has undertaken a national programme on the Human Genome that covers aspects such as: coordination of activities, sequencing and ADN mapping, disagreement of data-processing systems and people's training and education, and transferring of information. As for the ethical implications aroused by genetic research, the French option considers that it is of prime importance to set up internal debates in which all social sectors are represented. In this sense, the author points out that French policy can find no current justification for germinal modification work, and will encourage the principle of genetic non-discrimination. At the same time, it points to the need for a differential ethical discussion on the possible solutions that could be suggested.

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The French Government has undertaken a national programme on the Human Genome that covers aspects such as: coordination of activities, sequencing and ADN mapping, development of data-processing systems and people's training and education, and transferring of information. As for the ethical implications aroused by genetic research, the French opinion considers that it is of prime importance to set up internal debates in which all social sectors are represented. In this sense, the author points out that French policy can find no current justification for germinal modification work, and will encourage the principle of genetic non-discrimination. At the same time, it points to the need for a differential ethical discussion on the possible solutions that could be suggested.

It is a great honour for me to have been designated by the Presidency of the French Republic to attend your meeting and to present French national policy. It is a great honour, but it is also a great challenge to have the opportunity to speak in front of famous scientific workers: because even if I am a physician, formerly a professor of medicine, I am not at all a specialist of ethics. I am not at all a specialist of Human Genome, of genetics; I may be a specialist of national policy, being in charge, in the Ministry of Health, of the general policy for public and general health. If I comment on that position, it is just because obviously that is relevant for the meaning of the choice French authorities at the highest level had to attend and confront in that meeting.

My first duty is obviously to thank the foundations who organised the workshop, and the organising committee, for having focused this second workshop on ethics, which is obviously one of the major issues. Ethics of course, at least in France, is one of the most important tasks relevant to the interface between science, politics and democracy. The fight for human rights and dignity will be completed, and we do know risk coming from several sides –social, economic, political sides– and let's be frank; science could well support a risk if we are not cautious.

On the other hand –and this is a second reason to put the ethics debate in the front scenes– relations between science and society were not always easy, and not only in the past. One of the good reasons for developing ethics is the good opportunity, and probably the best, for scientific workers to communicate with society. And probably all these preliminary remarks are of most powerful signification when related to the Human Genome.

The place of ethics for politics in France was illustrated in the very early eighties, when the French government implemented a national committee in 1983, which is a kind of consultative committee –an ethics committee– for life sciences and health. This committeee, composed of 15 scientific workers, 15 people from society, and 5 representatives from the most common religions in France, is, as I mentioned a minute ago, a consultative one. But obviously, nearly 8 years later, it became a reference, which of course will not supplement the Parliament, but which has obviously permitted, and even induce, an internal debate, which for us is most important.

This committee has positions and makes statements on general matters which arise from scientific progress in the last years, such as prenatal diagnosis, grafts, and non-profit form tissue and cells and everything from the human body. The national committee also makes statements on embryo research and it is in that general background, that the committee is now facing what is to be discussed from the Human Genome and ethics.

Recently, in October 1990, the French government decide to implement a national programme for Human Genome, which is mainly a programme to coordinate national activity and international activity. Of course several teams have already been working for several years on human genome aspects, and the problem obviously is to coordinate this activity, first inside France and then outside. And money has been put into that coordination programme, amounting to 10 million dollars for 1991 and 20 million dollars for 1992.

Another aspect of the programme besides the coordination I mentioned a minute ago, is sequencing of DNA, that is mapping of course, and we know the relation there is already between Le Centre d'Etudes du Polymorphisme Humains, chaired by Jean Dausset and the Imperial Research Fund in the UK. Third, after sequencing and mapping, processing data systems will have to be developped. But also the genome analysis of small genomes will be carried on and completed in some examples.

Next, the training and education of people and transfer of information, which so far seems the most important task, to permit and to induce dicussion and general debate between scientific workers and the nation. Obviously, as I have already mentioned, the debate on the Human Genome is probably one of the most critical ones to raise the question of ethics and what that means...

We have the obligation to open the discussion far away, in little circles –important ones but little ones. If scientific workers, with philosophers, with judges and with social workers, are the only ones to discuss these critical matters, I think we will have tremendous difficulty in going through what all the scientific knowledge from the Human Genome could bring to human society.

I listened to the remark on the different approach if you compare the United States and Europe. I don't believe we can say that we are conducting ethics and science in the same way in Europe, as in the United States where they started off but it doesn't matter what happened in previous years –from now on, we really have to share both points of view. You claim that scientific workers are as able as others to discuss these matters, well, not quite; for scientific workers are may be not quite like ordinary citizens when it comes to discussing them. We bring something which is, of course, unavoidable, that is scientific knowledge, but are we sure we are quite neutral, being scientifically involved in these matters?

These are the discussions that are running in France at the moment, and it is my task to mention this, maybe so that we can talk about it later, and also to be a little provocative with scientific workers. Obviously, at the moment, even if we have some

background in ethical debate in France on an official basis, those questions concerning human rights and dignity and concerning human genome ethics, are not quite clear. They are just starting to be clear; the answers, of course, are not. Maybe the answers which are becoming clear are those which were debated in both France and the EEC, and in one way I regret that the EEC is not itself represented in this work group, to give a talk on what was decided in Brussels several months ago, when the Ministers of Research had a meeting in March 1990 to discuss such matters. But surely some people present could comment on what was said at this meeting.

First, obviously, as somebody mentioned, genetic injustice does not mean and dos not justify genetic discrimination. Two, there is no justification at the moment for working on germinal modification. Three, there is, at the moment, justification for working on somatic modification.

That is for Europe, and for France it will probably be enhanced when the National Committee for Ethics convenes in December for the 1990 session.

But besides this problem, besides these aspects, which are at the centre of French policy on ethics and the human genome, obviously some other points have to be discussed; I mean prenatal diagnosis, which obviously has three different patterns: prenatal diagnosis for those harmful diseases which are present from the very beginning of life, or even in utero, that is the first group. The second one, which arouses a different ethical discussion, is the diagnosis of those diseases coming later on his life, at the age of 40 or 50. And the third group of course is the group of diagnosis which will focus on the probability of disease, according to some other factors linked to these.

We think we must make a very clear distinction between these three groups of situations, and we have to go further on an ethical basis to know where to go and where not to go. We can't really discuss and debate ethics and the human genome without pointing out some secondary aspects, as: 1) the relation between forensic medicine and genetic treatment, 2) the confidentiality of information from human genome and genetic equipment, which in our view should be protected by medical secrecy just as any other medical information. We can also have a discussion on economic and commercial consequences of these questions, with budgetery consequences to be compared with other purpose as echography on a huge scale for diagnosis of morphological abnormalities.

I think of course that we have no choice; we have to perform both things, and we know that the knowledge which will arise from the Human Genome Project, is one of the most triggering new features in biological sciences, and for the human species.

I apologise speaking a language which is not my mother tongue, on some topics requiring very critical nuances, but the democratic power or our debate is something to be shared with everybody –with politicians, but also with everyone next to us; that is one of the main possitions in France. Thank you very much.

A GERMAN POINT OF VIEW

Hans Martin Sass

Director of the Centre of Medical Ethics in Bochum. Director of the European Programme of the Kennedy Institute of Ethics, Washington, DC. President of the Department of Philosophy of the University of the Ruhr, Bochum (Germany)

ABSTRACT

With the historical antecedent of Nazi-ism and under pressure from strong, so-called "alternative" groups, German scientific policy thought that it was important to come to public agreement on the legal and ethical implications of the application to people of genetic technology. To this end, different national committees have drawn up different reports in which, apart from acknowledging the advantages offered by genome analysis, general guidelines are given which reject a predictive medicine with eugenesic aims and which favour specific vigilance in precise areas of use and abuse such as pre-natal diagnosis, diagnostic testing related to employment and both civil and penal law-cases, protection of data and privacy.

The scientific community, the author says, must promote all types of differential ethics. With this aim in mind, he ends with the presentation of a methodological procedure, based on differentiation, assignation and evaluation of specific cases, which from the moral and ethical point of view facilitates discernment between the benefits and risks of genetic research.

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In Germany, Human Genome Projects have been discussed under two perspectives: the social acceptability of gene technology in general and the eugenic aspects in particular. Given the historical background of Nazi experimentation and the existence of strong so called 'alternative groups', well connected to the media, public concern has been voiced in regard to moral risks associated with the projects and discussed under 'worst case scenario' perspectives. Even the use of the term 'gene', alike that of the term 'repro', which stands for reproductive medicine, causes oversensitivity and hiperirritability in some sectors of society and the media. Amid a basic technophobic attitude towards new forms of high tech, special fears have been expressed in regard to future discrimination of the retarded and handicapped, discrimination in the work place and in the health care and insurance systems and an increase in selective abortions following predictive prenatal screening.

My presentation on the German debate summarizes (1) the development of consensus formation in public policy, (2) the alternative group arguments against genome project and consensus formation, (3) professional and academic bioethical debates regarding the Human Genome Project.

German science policy and the Human Genome Project

Science policy in the Federal Republic of Germany, since during the last years has recognized the importance of anticipatory moral debate and public consensus formation in regard to the development and introduction of new technology. In 1983 the BMFT (Federal Ministry for Research and Development) Minister Dr. Riesenhuber invited a diverse group of experts to discuss ethical and legal issues of applying gene technology to humans. Shortly thereafter an enquete commission of the Bundestag was established and published its report 'Chances and risks of Gene technology' in 1987. The German Research Foundation (DFG) and the Max Planck Society (MPG) introduced programs for social and moral assessment of research and sponsored conferences and publications. The new approach by Minister Riesenhuber indicates that the executive branch as well as the legislative, and research funding institutions in the Federal Republic have learned from political and moral mismanagement of the nuclear debate in Germany by encouraging public ethical debate prior to introduction of new technology.

In 1987 an enquete commission of the Federal Parliament issued a report on 'Chances and Risks of Gene Technology' (Bundestagsdrucksache 10/6775). The report discussed different scenarios of social and moral acceptability of gene manipulation, including Human Genome screening. The reports recognizes

diagnostic benefits of genome analysis and recommends to discuss different scenarios, particularly those in prenatal screening and in the work place, separately. Recommendations include nondirective counseling, non-eugenic use of new technology, cooperation with the medical profession to develop a catalogue treatable diseases for prenatal screening and for self-regulation to disclose only non-treatable severe anomalies or diseases prior to the 12th week of pregnancy, the development of binding legal parameters and employer-employee cooperation for genetic screening in the work place (Sass, 1988).

A joint Bund-Laender commission of senior executives from state and federal government, in May of 1990, issued guidelines refusing general prohibition of genetic screening and favoring specific oversight in regard to specific areas of possible use and abuse: prenatal screening, screening in occupational health, and in civil and penal court cases, protection of data and privacy. For prenatal screening the legal and voluntary access to screening, the trias counseling-screening-counseling, no screening to totipotent cells and screening of non-totipotent trophoblast cells only after clinical safety standards have been developed, non-directive and non-acute counseling, special licensing for screening physicians, limited screening for severe and un-treatable anomalies and diseases (no official list of such deseases shall be provided), costs paid by statutory or private insurance, restricted information to parents prior to the 12th. week of pregnancy, particularly regarding the sex of the fetus, no official large scale screening for non-treatable diseases. Screening in the work place may not include general DNA diagnosis (chromosomal and protein chemical diagnosis only for diseases or risks related to the particular work place), informed consent of the employee (illegal screening programs are illegal even when consent is obtained), no preventive DNA screening but specific chromosomal and protein screening for early detection of occupational health risks. No general screening is allowed for those applying for health care or life insurance, specific screening for diagnosing visible or otherwise diagnosed risks may be done. The legal system may not do screening for coding a person, other specific screening for search or in forensic medicine (DNA fingerprinting) may be done.

These guidelines mark an important consensus in German public policy and will determine the future course of regulation, self-regulation, legisltion and employer-employee cooperation (Buelow, 1990; Sass, 1990a). They are supported by powerful groups in society and political parties, except the Green party. The Green's politics "is directed against the concepts of biology and medicine which apply genetic engineering in a attempt to merely repair social and environmental problems. Genetic engineering techniques are the product of a relationship to Nature which is based on exploitation and domination rather than sustainability. This is true not only for applied research but for basic research as well; with the advent of genetic engineering, both are be-

coming increasingly directed by the objetives of accelerating industrial utilization of Nature... *We are demanding an immediate halt to all genetic engineering research and to all related applications and forms of production.*" (Die Gruenen, 1986, p. 2)

In July 1990, the German Genetic Engineering Law (Gengesetz) including five related regulations came into force and supplements the recommendations of the Bund-Laender group in ensuring protection against risk and dangers arising from recombinant nuclei acids constructed in vivo.

German federal government (Bundesregierung) and the federal parliament (Bundestag) support the European Genome Project. The first draft of the EC Predictive Medicine Project (COM (88) 424 final -SYN 146, July 20, 1988), however, caused a stormy debate in the federal parliament as all positions, including the federal government had problems with the semantics of the project and its possible eugenic consequences. In particular, the wording "Predictive Medicine seeks to protect individuals from the kinds of illneses to which they are genetically most vulnerable and, where appropiate, to prevent the transmission of the genetic susceptibilities to the next generation" (l.c., 1.1) was interpreted as introducing a eugenic public health policy for entire Europe. While all parties, except the Greens, and the government, were in favor of possible diagnostic benefits, all positions criticized possible or real eugenic ideology and intention of the program, the wording and focus of which was subsequently changed. It was asked whether the program would later call for a "eugenic oriented European medical and health policy and mass screening,... a European abortion program motivated by eugenics" (Seesing), also, whether "we Germans, in the light of experiences during the years 1933 through, should be sensible, even supersensible" in regard to the protection of human rights and human dignity (Catenhusen); Minister Riesenhuber pointed out that germline intervention should not be accepted and genome analysis should not be used for health policy based on eugenics, also, that voluntariness and data protection should be essential (Deutscher Bundestag, Plenarprotokoll 11/122, 8938-8943, Jan 26, 1989).

Alternative groups argumentation against Human Genome Projects

The alternative scene, a strong promotor of anticapitalist ideology, recognized the potentials of the eugenics debate when they prevented Peter Singer, the Australian bioethicist, from speaking as an invited guest at conferences in Germany in 1989. Singer, in one of his books, had discussed active euthanasia of severely defected newborns. These agitations turned the discussion regarding selectively withholding treatment from severely handicapped newborns into a debate of free speech. Singer, in a bitter

article, describes his experiences with free speech and academic discourse in Germany in this year's first issue of 'Bioethics' (Bioethics, 4, 1990). The Singer debate resulted in the development of subcultural networks from the extreme right to the extreme left, iniciating a campaign 'gegen Gen und Repro', i. e. against gene technology and reproductive technology. The annual meeting of the German Society for Anthropology and Human Genetics was canceled in 1989 due to threats from alternative groups and other internal problems. The Bochum Center for Medical Ethics later in 1989, nevertheless, proceeded with an international workshop on ethical issues regarding the Human Genome Project and human somatic cell gene therapy. The local student organization and groups associated with the Evangelische Studentengemeinde (local Protestant student union) threatened to intrude and upset the meeting, but finally accepted the invitation to attend and to get involved in the discussion. In the pretext of the meeting the students imputed that the conference's prime and exclusive goal was to develop an acceptance strategy (Akzeptanzstrategie) for undiscriminating human gemone manipulation, for discrimination in the work place and for discriminating against handicapped and disable citizens. They imputed that all discussion on genes would necessarily be a discussion on eugenics, i. e. advocating and promoting eugenics.

In June 1990 the European Society for Philosophy of Medicine and Health Care (ESPMH), the professional organization of European bioethicists, was scheduled to hold its 4th. Annual Meeting at the Bochum Zentrum fuer Medizinische Ethik focussing on 'Consensus Formation in Medicine and Health Care', a rather non-controversial methodological theme. Nevertheless, the regional and national 'alternative scene', including leading left wing journalists, decided that these activities of the Bochum center and its projects in differential ethics had to be put to an end. They started the defamation campaign against 'bioethics' in general and called for preventing the meeting to take place: "It is mandatory to prevent, that under the cloak of tolerance, democracy, and liberalism, strategies of annihilation can be discussed. This is the reason, that we will prevent the Bochum congress". (Sass, Viefhues, 1990, p. 43). A so called national network, led by the Genarchiv in Essen (gene archiv) and an ad-hoc Anti-Euthanasia Forum Ruhrgebiet (anti euthanasia forum ruhr area) organized Widerstandstagungen (resistance meetings) and prepared for interrupting and harassing the meeting of the ESPMH. The nationwide journal 'Konkret' (no. 5, p. 22) edited in Hamburg, in its June issue announced a series of alternative group activities: June 1-3 in Cologne, 'Congress of the Radical Left' (Kongre· der radikalen Linken), a 2 1/2 day teach-in on topics such 'never a new Germany again', 'anticapitalistic ecology and perspectives of resistance','eugenics', speakers and panelists including feminists, left-radicals, kommunists, ex- and still Greens; a one day conference June 9 in Kulturzentrum Bochum Langedreer on 'Deadly Ethics' (Tödliche Ethik), one of the topics was: how to prevent the

ESPMH meeting. The ESPMH meetings in Bochum were moved from Bochum to Maastricht. The board of the ESPMH, in a letter to the ad hoc committee of experts in bioethics of the European Community (CAHBI), June 18, 1990, called the events "a violation of basic democratic principles", and complained about "the shameful fact... that the basic democratic principles of freedom of assembly and freedom of speech could not be upheld in a University town in the Federal Republic of Germany, and we feel that the occurrence of this incident must be made publicly known. We feel sure that the vast majority of the German people will agree with us that it is contrary to their interests and to the interests of all Europeans that academic societies such as ours are forced to avoid holding our conferences in the Federal Republic of Germany" (Saas, Viefhues, 1990, p. 29f).

The "alternative" strategy of dialogue refusal is based on mistrust towards the "entire establishment", a suspicion against a presumed "cartel of organized interests", imputing class interest guiding without exemption the positions taken by all speakers and conference participants. An article in the May/June issue of 'Boriss', a Bochum student journal, puts the thesis, that the method of assessing and balancing goods and moral goods (Gueterabwaegung) sounds good on paper only, but will not work when it comes to real-life issues, because personal and group interests will prevail, such as those against the burdens of caring of paying for handicapped and disable citizens, and necessarily will prepare the road for euthanasia. Therefore the author supports the "supraregional coalition of groups of the retarded and the crippled, feminist groups, enemies of genes and reproduction" in its efforts to prevent the conference of "philosophers calling themselves bioethicists discussing euthanasia, methods of reproduction, and death criteria" (Sass, Viefhues, 1990, p. 35f). Bioethics is defined as "ethics of technocrats", a new "form of research in acceptability", or "services ethics", serving to "provide acceptance for risky technologies, in order to promote easy introduction of a health policy ready to accept dead persons and the realization of cost-benefit based calculations of killing utopias" (l.c. p. 36).

The author concludes, that the ESPMH meeting scheduled for Bochum "has to be assessed as a contribution to further introducing bioethics into Europe and particularly into the Federal Republic", with the intention "or further suppression of critical assessment of gene- and reproductive technologies or of a health policy exclusively oriented along economic criteria".

I do not think that the 'alternative groups' represent a dominant force in West German society, on the contrary. But in the absence of a differentiating media debate and public discussion on issues of moral concern in medicine in particular and technology in general, they are capable to organize impressive support for ad hoc actions. For those ad hoc actions, they eventually might also get support of a nationwide hard core of

violent anarchists, muffled rowdies, terrorists, and toughs. Nevertheless, the arguments voiced by these groups reveal a cultural and political attitude of a potentially growing number of so called alternative individuals and their groups who have lost their basic trust in society and who have become suspicious even against those, who work hard to give their best in analyzing and assessing the wrongs and pitfalls of modern medicine, modern technology, of technocratism, economism, and bureaucratism. They do not represent, as they claim, an alternative to the existing society, rather the far out edges of a society based on a fabric on cooperation, mutual trust, and solidarity, for which dialogue and open and fair discourse are essential. In refusing the discussion and in threatening to actively preventing consensus oriented discussions, the destroy the fundament of societies based on mutual respect, discourse, and cooperation. In targeting the human genome project and other issues which include moral risks and dangers, they are not directly interested in the issue itself, rather use it to present their particular vision of an alternative world, for agitation and network building among the dissatisfied and frustrated. Some of these groups, such as the Greens, follow a double strategy of involvement in the societal network of allocating and deciding on the one side, while on the other hand criticizing and violently attacking the 'system' from the outside.

Academic and professional bioethical debates

Irrational and ideological outright and general refusal of Human Genome Projects is a challenge not only to the fabric of a society based on communication, dialogue and mutually shared values, but also a challenge for the professional community of scientists, physicians and bioethicists and their professional ethos. In arguing with these groups, more is at stake than academic freedom and freedom of speech. We need understanding, patience and endurance in not giving up to communicate with those who distrust all established forms of communicate and dialogue, who find security in internal emigration and in refusing communication, who prefer violence over dialogue, conflict over communication.

The agitations, unfortunate as they are, call for an increase, not an abandonment, of all forms of differentiating ethics in public discourse, in education, and in the professional and political settings. Only increased competence in differential ethics will enable individuals, professions, and societies to apply and develop technology in a prudent, ethical, and socially responsible way. The refusal of dialogue, the opinionated, stubborn and dogmatic refusal of certain forms of technology and of moral technology assessment will only destroy the social, moral, and finally political fabric of pluralistic and technology based societies.

Scientists and bioethicist have to play an important role in supporting differentiating public debates and decision making. As ideologists tend to argue very general only, it is important to be very specific in regard to very specific benefits and harms, to do moral scenario assessment case by case. As we do not discuss the moral benefits or harms of electricity, which include lightening, electric machinery, electrocution, electric torture, and make moral assessments pro or contra electricity based on worst case scenario vision, we may not discuss Human Genome Projects in general under the aspects of eugenic abuse or personal and professional discrimination. Rather, we want to discuss professionally and publicly its use for preventive detection of very specific health risks in very specific work places or for prenatal detection of severe genetic chromosomal heritage of unborn life at risk or for DNA fingerprinting of criminals. These scenarios offer high moral, medical, and social benefits over low risk and no harm. Other scenarios, such as routine general genetic screening of entire populations, coding specific individuals with long term health risks or prenatal sex selection present high moral harms and risks associated with minimal or negligible moral or social benefits. Open and pluralistic societies will agree on many good scenarios and on many unwanted and uncalled for; there will be disagreement in regard to some scenarios in the middle. But the differentiation between typical scenarios of use and abuse will help not only researches, physicians, and politicians, but most of all the educated individual citizen in assessing the benefits and limits of any form of new technology, including the technologies which allow us to identify, diagnose, and eventually heal and manipulate the Human Genome heritage.

The Bochum Center for Medical Ethics has developed a Scenario Development Procedure for moral assessment of specific new scenarios defined by new use of technology or use of new technology and complex moral conflicts (Sass, 1990b). The moral assessment procedure follows proven methods in technology assessment and risk analysis originally developed in complex technical or economic situations for risk reduction and risk prevention. The moral scenario assessment method avoids basic ideological or metaphysical weltanschauung discussion and confrontation. Its two first steps analyze and discuss moral and technical principles and facts establishing the framework of a specific scenario. The next two steps compare and assess scenario modifications providing different moral risk parameters and different moral benefit-harm balances. The scenario assessment method has proven to be a most effective forms of developing professional ethics expertise in simulating and anticipating real-life challenges to ethical expertise in the work place and in personal life. The use of methodologically refined moral scenario assessment procedures is of particular importance in pluralistic societies for developing expertise in complex and consensus oriented value assessment in concrete situations and for determining the course of action in applying, developing and stewarding new technology,

including gene technologies. For a morally responsible, politically prudent, and culturally comfortable acceptance of Human Genome Projects differentiating moral scenario procedures must be used in (a) consulting on public policy options, (b) professional scenario assessment, (c) anticipatory risk analysis, and (d) single case evaluation.

Most authors in the publication which came out of the mentioned Bochum meeting in 1989 (Saas, 1990), in assessing the probable moral and societal benefits, risks and harms of Human Genome Projects and human gene therapy, use the methodological approach of differentiating, allocating, and assessing mid-level moral principles and technical risks and uncertainties in concrete scenarios in discussing the moral benefits and risks of the Human Genome Project.

SCENARIO DEVELOPMENT PROCEDURE

1. PROBLEM IDENTIFICATION

   a) Collecting technical data.
   b) Collecting significant human data.
   c) Identification of value elements.
   d) Discuss relations between technical and human values.

2. DEVELOP ALTERNATIVE SCENARIOS FOR ACTION

   a) Establish reasonable possibilities for each scenario.
   b) Identify ethical principals in each scenario.
   c) Determine ethical costs and risks in each scenario.
   d) Discuss ethical and technical cost-benefit assessments.

3. PRESENT A SET OF ALTERNATIVE SCENARIOS

   a) Discuss uncertainty in each scenario prognosis.
   b) Present technical cost-benefit-risk assessments.
   c) Present ethical cost-benefit-risk assessments.
   d) Discuss differences in benefit-cost-risk balances.

4. FORMULATE A JUSTIFICATION FOR YOUR SELECTION

   a) Specify your reasons for the selected course of action.
   b) Clearly present the ethical basis for your action.
   c) Understand ethical shortcomings of your justification.
   d) Anticipate and discuss objections to your selection.

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A BRITISH APPROACH

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ABSTRACT

The author suggests that the meaning of ethics is not univocal and that by shielding themselves behind it, many could deprive mankind of the important benefits the Human Genome Project could contribute, a project which on the other hand poses no more risks than any other human activity. The efficiency of the project should be judged on the strength of the resulting equilibrium between benefits and drawbacks it may offer. The author moreover insists on the planning of the control of its possible dangers and this could be carried out at three leverls: professional ethics, legislative control and by means of international agreements.

The Human Genome Project in the United Kingdom is a modest one and importance is currently given to the work of coordination and facilitating research, as likewise to potentiating existing capacities and encouraging interest in British industry. It is also considered that any discoveries made should be public property.

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The Human Genome Project in the United Kingdom is a modest one and importance is currently given to the work of coordination and facilitating research, as likewise to potentiating existing capacities and encouraging interest in British industry. It is also considered that any discoveries made should be public property.

It is worrying that the word "ethics" has no single or simple meaning. There was an article in April's Scientific European about "Ethics and biotechnology"; I could see nothing in it that I immediately understood to be inherently an ethical issue.

I have used that particular example to try to focus my own concerns about the present debate. There is now a major ethics industry. Large sums are spent on ethical debate. It is self-evident that an ethical forum such as this is a challenge to identify problems. A cloud is created behind which those who –for whatever reason– wish to oppose investment in genome analysis can hide motives other than ethical concerns. If any lesson derived from the genetic manipulation debate of the mid-70s can be applied here, it may be that the real issue is complicated by the hidden agendas of the protagonists. The very word "ethics" is itself potent: if I oppose you on the grounds that your ideas or actions are unethical, I am claiming the moral high ground in a way that is only a little more sophisticated than saying you are "wicked".

I believe that studies of human genetics have a great positive potential that could be unnecessarily frustrated if too much ethical song and dance is made irresponsibly. As in most human activities, there is no doubt about the harmful potential in knowledge of genetics. If that latter potential could not be controlled, then we have a problem, but I remain unconvinced that that is the case.

The most pressing ethical question is whether it can be right to deny access to potentially available and affordable knowledge. By "affordable" I mean that the necessary money is there and there is no better way to spend it. But those are not ethical considerations. It seems a short step from the refusal of access to this new knowledge, because it *might* be misused (however that is defined or judged), to restriction of access to existing knowledge: to burning books and to censorship.

The effectiveness of the UK Human Genome Project will be judged on the scale and the balance of benefits and disbenefits that stem from the application of the knowledge that accrues. The Project itself has no inherent disbenefits. There must be no confusion with the debate 15 years ago about whether genetic manipulation, as a laboratory practice, might be inherently hazardous. The only role of the debate now is to define what disbenefits *might* result from the application or misapplication of the knowledge and, so far as is practicable, to be prepared to set up safeguards to eliminate unnecessary disbenefits and to limit unavoidable ones –if there are such– to some acceptable level. If there are major potentials for good, then the emphasis must be on

planning for control, to restrict questionable outcomes, not on whether the work should go ahead at all.

There are two obvious levels of control. I accept that the existing power of medical genetics raises questions of professional ethics –the relationship between doctor and patient– that have not been resolved. I see nothing in this problem that is qualitatively new or insoluble.

There is a second level –as illustrated by the release of genetically-engineered micro-organisms– where there are strong financial incentives to courses of action that are socially undesirable. Legislative control is the only possible solution.

There may be a third level of control by means of international conventions, of the sort appropriate for biological or chemical or nuclear warfare, if it is thought that states may misuse the knowledge.

The planning of the UK Project has had to take account of the relatively modest scale of support and of the possibility of a major US programme. The fact that ot 11 million was explicitly earmarked by the Government for this particular Project implies the importance (in terms of internal scientific politics) of developing, within the three-year initial time span, a significant UK position. The key to the UK programme is the selective expansion of existing strengths coupled with an effort to coordinate and facilitate all such work. It is self-evident that the present form of operation in UK molecular an clinical genetics is inefficient, in that a number of relatively small teams are looking for a few genes or needles –the ones that interest them– in a genetic haystack. A major strategic thrust in the UK Project is a systematic needle-picking exercise, to save time and effort and give workers a chance to get more directly into clinical and biological analysis. Another analogy would be with the sort of indexing system that gives you some idea what a particular book is about –and where it is on the shelves–. It is still up to you to find out whether the contents are really what you want, and do something with them.

Here is what I accept to be a major ethical consideration: that it would be morally wrong for the data deriving from genome mapping projects not to be in the public domain. That is certainly strogly believed by the UK scientific community. Our database will be a private one, in that it will hold only the outcome of our (and any collaborators') programme: a listing of the partially characterized fragments of genes we have pulled out of the haystack. But it will be public too. Workers will be able to have those frag ments as tools to map the genome; that in turn will further characterize the fragments, and those whose objective is genes rather than map-drawing will be able to have both any needle that looks interesting and the means to build up a picture of the complete

gene. One explicit condition will be that the resulting data themselves go into one of the public databases.

We are enjoined to further the interests of UK industry: the main commercial benefits will presumably come either from diagnostics or, at longer-range, from rational drug design. I see no problem in industry taking away data or materials from our collection. The condition, in any case, will be that the UK Project retains ownership of the original needles and, even if only as a formality, a say and a stake in subsequent commercial exploitation and that information comes back.

It is difficult to assess the existing level of support in the UK for the totality of work that might be helped by the UK Project; it can hardly be less per year than 3 times the annual amount being committed to the Project. What we have to increasing efficiency and effectiveness, the project money has yielded an increment in performance greater than was likely to have been achieved simply by spending the extra on "more of the same".

Whether this will work remains to be seen. If it does, then the positive consequences might be improved understanding of the mechanism of disease, not just those resulting from single-gen defects, better diagnosis and therapy, and more precisely-targeted preventive medicine. Each of those hopes generates some ambivalence. This inherent complexity of the issues may be a factor in damping down interest. There is no clear rallying point for, say, the anti-abortion lobby: better diagnosis of genetic defects might reduce the demad for abortions or might increase it.

The modest scale of the UK venture and the style of decision-making are two other possible reasons why the level of public interest is low: concerns, in so far as they surface at all, either do so in the context of the US programme or already exist, in terms of worries about on-going genetic research and clinical pratice. The perception, rightly, is that what we are putting into effect is a plan to do more of what is already going on, more efficiently, economically and effectively. So no new problems arise.

It would be regrettable if inhibitions in one country whether they arise from particular ethical sensitivities or from alarm at the scale of what is proposed –spilled over into others. That is one reason why the misleading impression of a single Human Genome Mapping Project should be avoided. A headline in the "New Scientist" shouting "What's wrong with the Human Genome Project" jars no less when it turns out that it is the US programme that is being criticised, and by an American: politicians respond to headlines. It seems best –as well as accurate– to see the current activity worldwide as representing a whole series of individual and independent programmes, within the context of a widespread perception that Human Genome mapping is a field ripe for development.

Some issues on the agenda for this meeting –for example the implications of genetic screening for life assurance or as a preliminary to employment– seem to be matters of social policy rather than ethics, and best dealt with in an evolutionary and pragmatic way. It may be that what I am accepting in that statement is that in practice ethical considerations are only material in looking at activities that are dispensable or where there are clear alternative ways to a given end: for example, research can be inhibited if it is painted as "unethical". But Governments have a wide range of acceptable freedom for taking action that damages individuals.

When any substantial advance in medical research is delivered into practice, in the context of inevitably limited resources, decision –perhaps life and death decisions– are implied that favour some persons at others' expense. Individual or group ethics are then displaced by tough corporate pragmatism; if they were not, the National Health Service would cease to operate.

The life assurance business, to take another example of corporate activity, is not there to act as a charity and there is no prescriptive right to life assurance. If the application of genetic advances means that more people than at present are deemed to represent high or even unacceptable risks, that raises questions such as whether the money the rest save by a more precise definition of the actuarial risks they represent should not be balanced by some extension of state underpinning.

In the UK, some, at least, of the ethical concerns I infer from the programme of this meeting are already the subject of statutory control (for example, the Data Protection Act, and the legislation governing embryo research, which will ban germ-line gene therapy) or of ethical guidance of greater or lesser force, from bodies such as the British Medical Association or the Medical Research Council. It may be innocent to say that those constraints are effective, but, to take the example of recent proposals for legislation in the US, to require written consent from an employee before his medical history is disclosed to an actual or potential employer, my understanding is that this is the well-established practice in the UK and, moreover, disclosure is limited to medical practitioners. In this context "ethics" really means an element of professional conduct: how, for example, medical data relating to an individual are handled by his medical practitioner.

Ethical issues, within a forum such as this, can be treated in a way that is both too subtle and overstressed. This problem has been compounded by the nature and scale of the US programme –at least as commonly perceived.

In aggregate, the expenditure of medical research charities in the UK exceeds the budget of the MRC; they are a potent force in determining what the research agenda is. Some are explicitly concerned with single-gene conditions such as cystic fibrosis and

muscular dystrophy; others –for example, those that deal with heart disease, diabetes, arthritis and rheumatism, cancer and some forms of psychiatric illness– now have a major interest and investment in genetics. So far as I am aware, none of the charieties has major reservations about supporting the objectives of the UK Human Genome Mapping Project. The general public in the UK are generous in supporting the work of those charities. Even more important, those who are directly affected, as sufferers and the relatives of those affected, are generally strong in support of pursuit of the cause of diseases. The robustness of the attitudes of those most directly affected is something that should not be overlooked. The response of a patient asked whether he will agree to 'his' cells being used for research is surprise that such ethical delicaty surfaces in the rough and tumble of normal medical routine. I suppose if I were seriously ill I might not be aware enough to feel degraded by being trundled in my bed through the main public corridors of a hospital, but that is a distressing sight I am exposed to as an observer every working day. Whether or not those patients' cells or DNA or whatever get into our laboratory seems an utterly trivial issue by comparison. What do "privacy", "confidentiality" and "informed consent" mean in that context?

There is all the difference in the world between, on the one hand, guiding the medical profession into handling individuals sensitively with awareness of the ramifications of complex issues and, on the other hand, taking block decisions on behalf of all individuals. The question whether my doctor should tell me if I have cancer or the gen for Huntigton's disease or whatever is one that in the last resort I want to answer. I feel strongly about that, but I feel equally strongly that others have a right to different individual views. I do not wish either to impose my own preferences on others or to have others prescribe what is "right" for me.

If the discussion at the present meeting extends positively to the formulation, not just of problems, but of solutions, in a form that actually meshes with the processes by which the solutions might be implemented, well and good. My apprehension is that the debate will abort at the stage where it does nothing but raise objections, and, moreover, that the same will be true the next time the issue is discussed, and the next time, and... And the danger is that governments will choose the easy option, which is to stop the research, not because the noise generated by the ethical debate looks more important –in terms of electoral calculations– than benefits that may be a long way in the future.

SCIENTIFIC AND ETHICAL ASPECTS OF THE HUMAN GENOME PROJECT IN ITALY

Paolo Vezzoni *

Istituto di Tecnologie biomediche Avanzate, CNR (Institute of Advanced Bio-medical Technology, CNR)

ABSTRACT

Within the scientific ambit of the Human Genome Project , Italy thought it preferable to potentiate existing centres and research teams. Moreover, it was decided to concentrate work on one specific genomic region: the terminal portion of the long arm of chromosome X, called Xq24-qter. Tunnel-effect microscope techniques are also being developed.

As for the ethical aspects of the project, an agreement has been reached in Italy, by which genotherapy of somatic cells is permitted, but not that of germinal cells. And as for the danger of any possible discrimination of bearers of abnormal features, it is thought that this could be regulated by laws and professional ethical codes.

* Paper written in collaboration with Elena Redolfi, Annalisa Frattini and Monica Repetto.

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* Paper written in collaboration with Elena Rakelli, Annalisa Pastini and Nicola Sapone.

I would like to thank the organisers for giving me the opportunity to speak about the scientific organization of the Human Genome project in Italy and about the ethical problems that can be raised in this area and the way it has been tackled in our country.

The Italian project started in 1987 and it was funded by the main scientific agency in Italy, which is the Consiglio Nazionale della Ricerche (National Research Council, CNR). The Nobel Prize Renato Dulbecco, an Italian scientist which is now President of the Salk Institute, was asked to act as coordinator to provide scientific advice and to ensure the internationality of project, since we felt from the beginning that this project should be carried out only in a international context.

For the first three years we have allocated about 1.7 million dollars for each year in a program that was evaluated year by year. Now this project has been inserted in a wider project on molecular biology that lasts from 1991 to 1995, and in this way the survival of the project has been assured for at last 5 years with the same amount of about 2 million dollars. If it is taken into account that these figures do not include salaries for investigators, it is possible to see that, even if they cannot be compared to the amount of money that is spent in the United States, they are in the same order of magnitude as other European initiatives.

It was decided that the project would focus on a single specific region, that is the terminal portion of the long arm of the X chromosome, and instead of building a new centre for genome studies, we tried to potentiate existing units already working on the genetics of this chromosome or plannig to work on technological developments on mapping and sequencing, since it was felt that technological advances were absolutely needed to carry on this project.

Table I summarizes some of the research aspects that have been carried out under the aegis of the project as well as some published results already obtained. The table shows also some international collaborations that have been set up in the framework of the project, since we strogly think that larger benefits to the scientific progress can come from cooperation in this area.

In this regard we will mention here only the collaboration between italian researchers and the Washington University in St Louis, that led to the construction of a YAC library from the cell line X.3000.11, a human/hamster hybrid containing the chromosomal region Xq24-qter as the only human component. Under the direction of Dr. D. Schlessinger a lot of work has been done in mapping this genome region with this powerful new tool, as will be discussed in Schlessinger and D'Urso papers in this same meeting.

Table 1: Partial list of activities of the Italian Human Genome Project and of the international collaborations.

Mapping, YAC vectors (1, 2)	Dr. D. Schlessinger, St. Louis, MO
Mapping, traditional vectors (3-6)	Dr. J. L. Mandel, Strasbourg, France
	Dr. G. Evans, La Jolla, CA
	Dr. F. Giannelli, London, UK
	Dr. A. Ballabio, Houston, TX
In situ hybridization	
Automation (7, 8)	
STS map of the Zq24-qter	
Scanning tnneling microscopy (9)	
Computer sequence analysis	Dr. N. Kolchanov, Novosibirsk, URSS
Ethical evaluation (10)	
References	
1) Wada et al.	*Am. J. Hum. Genet.*, 46:95, 1990
2) Little R. et al.	*Proc. Natl. Acad. Sci.*, 86:1598, 1989
3) Ballabio A. et al.	*Genomics*, 8:263, 1990
4) Maestrini C. et al.	*Genomics*, 8:664, 1990
5) Manoni M. et al.	*Genomics*, 9:553, 1991
6) Rousseau F. et al.	*Am. J. Hum. Genet.*, 48:108, 1991
7) De bellis G. et al.	*Nucl. Ac. Res.*, 18:4951, 1990
8) Carminci P. et al.	*Nucl. Ac. Res.*, 18:204, 1990
9) Cricenti A. et al.	*Science*, 245: 1226, 1989
10) Brovedani E.	*Aggiornamenti sociali*, 40:487, 1989

In addition, the construction of conventional phage and cosmid libraries from the same hybrid has led to the production of many useful clones that have been used in linkage analysis and physical mapping. Some clones have been mapped to chromosomal bands and are currently investigated for association with genetic diseases. In situ hybridization with non radioactive probes has been extensively used to map YAC and other clones.

Another program pursued in the framework of the project is the construction of an STS (Sequence Tagged Sit) map of the Xq24-qter. The main feature of this approach is to sequence small pieces of DNA mapping in this region and establish their order along the chromosome, as proposed by Olson and coworkers in 1989. The choice of segments for STS map could be completely random, but we plan to sequence fragments close to the so called CpG islands. In this regard, Eag I site containing clones have been obtained by constructing a specialized library and by subcloning cosmids digested with rare cutter enzymes, mapped to chromosomal bands with a panel of hybrids and sequenced with automated devices. The advantage of this CpG island-based map is that the deriving STS map is, at least in some way, gene-associated.

A completely new approach to the analysis and sequence of the genome is also investigated in the project. This program is based on a new technology, the scanning tunneling microscopy. Direct visualization of the double helix of DNA is obtained ( ) and it is not impossible that in future sequences could be obtained with

these means. This would allow to increase the speed of sequencing that is really needed if we want to extensively sequence the 3 billion nucleotides-long human genome.

Ethical problems associated with this project have been discussed from the beginning. Definition of all the genes of the Human Genome could provide better diagnosis and perhaps therapy of many genetic diseases, and everyone agrees on the potential benefits for the mankind that can derive from the Human Genome Project. There are however several aspects of this research that deserve careful evaluation. Among them we will discuss briefly two problems: gene therapy and results disclosure.

As far as gene therapy is concerned, a wide agreement has been recently reached on this matter by a panel of experts including scientists, politicians, ethicists as well as theologians from the Roman Catholic Church. The panel recognized the liceity of somatic cell gene therapy since in this case the therapy does not differ in priciple from other kinds of therapy, for example bone marrow transplantation; germ line gene therapy is not allowed for the moment, since the potential benefits are counterbalanced by the possibility to harm the embryo (especially by insertional mutagenesis that occur frequently in transgenic mouse models); in addition, there are fears that these techniques could be used for changing the Human Genome.

Disclosure of genetical tests for employment as well as for medical and life insurance is another possibility. Contrary to what happens in United States, access to medical insurance is not a problem in Italy since health care is all government supported and nobody can be excluded from health care on the basis of genetic diagnosis.

Disclosure of results obtained with new genetics techniques could be used to discriminate people carrying an abnormal trait manifesting itself only later in life, as it happens in Huntington's disease, both in employment and in life insurance, but it is felt that again these informations are not very different from other information already available with other conventional means (for example, predictive tests for predisposition to diabetes). This area can be easily regulated by law, keeping in mind the old medical rule of professional secret. In addition, it is not impossible to think that in future individual life insurance becomes a general feature supported by the state.

In conclusion, the Human Genome Project in Italy is now well established, even if not in the large scale as in United States. No big Genome Centres have been established, but small existing groups have been encouraged to work focusing on a definite portion of the Human Genome. In some aspects the money allocated for the project is new money for genetics research community and the project will greatly benefit both basic and applied genetic research in Italy.

POLICY IN RELATION TO THE HUMAN GENOME PROJECT. THE VIEW FROM THE USSR

Alexander Bayev

Engelhardt Institute of Molecular Biology, Academy of Sciences of the USSR, Moscow

ABSTRACT

The ethics developed in the USSR has been impregnated with orthodox Marxism and has had a strong political component. At present, ethics and morals are guiding Soviet society in a more human way. Today, the Human Genome Project is also being developed in the USSR, besides being the first in this field of human genetics. The scientists in charge of the project consider that it will characterize man as a species and not as an individual. Other additional methods of analysis are required to this latter end. Therefore, it would seem that the possible influence on society of knowledge of the human genome, and also on the destiny of man, would be the final stage of the project on a far more long-term basis. Yet in provision for the future Soviet scientists consider a person's genome to be his or her own exclusive property, as part of human rights.

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The standards of ethics and the code of morals are historical categories and depend on a social environment which creates them and where they operate. Religious *Weltanschauung* lays claim to their absolute importance although, if one takes an unprejudiced attitude, their historical origin becomes obvious. The moral principles of Christianity and Judaism are different inspite of their common history and succession.

The interpretation of morals as a historical and social phenomenon justifies analysing the morals of our Soviety society in relation to human genome studies. This is not a simple enterprise, but one can try to overcome the difficulties along this route.

It appears to me that the ethic developed by our philosophers has not ignores its universal history and values procured by the work of great intellects in the past. Yet the spirit of orthodox Marxism governs this ethic and it always obeyed political orders, which made it so peculiar and accounts for its decline [1]. The proponents of this ethic claimed that its standards and the code of morals were entirely dependent on historical-social factors and that ethical principles had a class and political character.

Marxism advocates that the class capitalist society must eventually become a more perfect classless society and the class morals must give way to a classless ethic common to all mankind. Marx held that this would be done by the proletariat, i.e. the working class, by seizing power and via its dictatorship. This dogma was officially adopted in this country after the October Revolution in 1917 when the first state of workers and peasants was declared. Later on, after WWII, this definition was extended (but again not always) to "the people's intelligentsia" (that is not the whole intelligentsia, but a part of it, which has never been defined precisely: what does "peoples" mean in this contest?). Now, in the era of *perestroika*, the official phraseology has invented a new term, "a man of labour".

All what I have said above is directly associated with the problems of morals since the Soviet society was artificially segregated into (1) workers and peasants who were claimed to enjoy full rights and the benefits of this moral code, and (2) all the others who were deprived or social rights.

For a long time the ethics of our society was ouvertly utilitarian. Not that the concepts of good and evil, kindness and harm, conscience and honour did not exist, but they were ruled by political orders and the only criterion for them was to benefit the revolution and the dictatorship of the proletariat.

The actual reality was even more biased. The state of workers and peasants was nothing else but a propagandist slogan because the workers were exploited in this society whereas the peasants were not only exploited but even destroyed (collectivisation). In

fact, the Soviet society was tyrannised by a small oligarchical group of party leaders headed by Stalin, and the state morals served the interests of this group who dictated their ideology and the standards of behaviour.

The situation in the corridors of science was complicated by the dictatorship of political leaders and, particularly in the field of genetics, by the dominion of Lysenko and his agrobiological ideas [2]...

Now the situation has changed drastically. Although the oligarchy is trying hard to thrust beneficial to its ethical standards on our society, this does not work. The society lives now by the code of morals advocated by Russian intellectuals in the past and in the present as well as according to the traditions of Russian history.

The universal principles of ethics and morals again guide our society now. It is in their terms that the problem of Human Genome studies is considered now. Radical political and economical reforms in our country (perestroika) have modified the *Weltanschauung* and, in particular, the ethic standards. This is not a Dr. Jekyll and Mr. Hyde phenomenon, but a profound alteration of our way of thinking forever.

The state policy and social trends are humane now in a pleasant contrast to the past. The programme Human genome is an integral part of ideas and actions prevailing nowdays in this country.

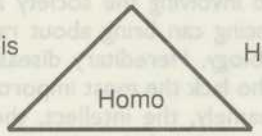
The USSR had no comprehensive programme of Human Genome investigation till 1989, and the present project is the first one in this field [3].

The programmes of studying Human Genome are primarily aimed at its mapping and sequencing. Yet genome analysis cannot be confined to this purpose although its realisation will throw more light on genome architecture and possibly reveal many secrets buried by the nature in its wonderful creation.

Chemical symbols *per se* are dead and must necessarily be compared with functions, with dynamic factors which we understand as the meaning and concealed essence of life. Functional decoding occurs now, too, but it will become more comprehensive and effective as structural information is being accumulated. Functional decoding is a second, probably even more important and difficult, problem in the programme of Human Genome studies. We should learn how to read structural texts of Human Genome in terms of functions, I.e. pass from the syntax of the genome to its semantics. Only in that case our knowledge about Human Genome will be useful and capable of influencing the social and moral-ethical aspects of human existence. However the comprehension of Human Genome must pass through yet another stage before it becomes capable of influencing the society and its individuals.

What shall we get as a result of sequencing Human Genome at the first step? The sequence of chemical symbols (it does no matter within this context whether they are decoded or not) can be considered merely as a model of Human Genome belonging to none of human individuals in the past, present and future. This depends on the method of sequencing developed by the universal association of researchers. The material for analysis is obtained not from a particular individual, but from quite different sources, and the analysis is done by various scientists so that analytical error are unavoidable. That is why a sequence obtained after 10-15 years of common tireless efforts may be considered only as a model of Human Genome as a species, and it will be used as a standar in the future.

This situation can be illustrated by the following scheme:



The model of Human Genome created as a result of the programme will characterise the man as a species (*Homo sapiens*). The characterisation of an individual (*Homo individualis*) requires a special method or methods, something like fingerprinting, to describe the most important features of an individual genome. The individual differences of Human Genome are rather small in terms of its composition: 0.1% or ca. 3×10^{6} bp for two unrelated individuals. However these differences are intensified by greater sequence modification caused by rearrangements, inserts, deletions, etc. Then the comprehension of Human Genome enriched with functional ideas will make it possible to characterise real human beings, with all their individual biological properties under the conditions of their social environment (*Homo civilis*).

Only at the last step, scientific ideas about Human Genome will be able to influence its social status and personal destiny. And here we shall face a great number of situations.

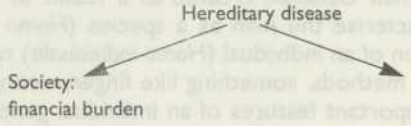
Let us first consider possible effects on the society as such. We should hardly use here the abstract concepts of good and evil: it would be easier to stand on the ground of utilitarianism and employ the criterion of public well-being and benefit.

Once of the possible consequences in decoding Human Genome may be concerned with another outburst of eugenic ideas, presumably similar to those put forward in the past. There is no doubt that the advocates of eugenics will try to take nucleotide sequences as objective criteria for claiming some individuals,

groups and races either superior or inferior. The appeal by German nazi for race hygiene because of the Nordic race superiority were mostly based on mystic concepts. The adherents of eugenics held that genetic factors exerted an absolute effect on mental development, moral status, criminality and drug addiction.

The possession of a model (standard) genome, the possibility to characterise an individual genome and to interpret it in functional terms will, no doubt, tempt some persons to use this information for eugenic deductions. That is why we may expect a new outburst of eugenic ideas and old mistakes repeating themselves nowdays. This is even more possible now because human survival becomes a real problem and eugenics can be used in the struggle for existence rather than for ideological purposes.

Hereditary diseases are another problem associated with Human Genome studies and involving the society as a whole. Genome mapping and sequencing can bring about radical changes in this field of human pathology. Hereditary diseases sometime engender human beings who lack the most important properties of this biological species, namely, the intellect, the capability to work and to enjoy life. Supporting their existence on merciful grounds is a heavy financial burden for the society. The birth of such a baby is a an infinite misery for the family.



Yet even less serious manifestations of hereditary pathology often are hard to cure, make the patient physically disabled and, at the late stages of pathology, create the feeling of doom. We may hope that the programme of Human Genome studies will allow us to comprehend the pathogenesis of hereditary diseases, to improve their diagnostics, to prevent and to cure them, thus making a social contribution to social benefit.

Anyway genetic problems become more and more acute and important as the environment is destroyed and polluted at an ever increasing scale, the industry and population density rise, and the programme of Human Genome studies may help to solve them.

Now I would like to say several words about how this programme relates to an individual. As I has noted above, it will be possible sooner or later to pass from a genome model to individual genomes and to construct an individual genetic portrait. We may only guess now what this portrait will be and how closely it can describe the original. Apparently, at the beginning, it will contain only a few available genetic characteristics, but gradually more of these will be added to it.

This portrait may warn us against possible diseases, indicate mutant genes threatening with hereditary diseases in descendants, contain a predisposition for diseases, psychopathology. Moreover, it can include information characterizing not human pathology, but such factures of the individual as its behaviour, emotions, inclinations, intellectual potential, etc.

All these characteristics relate to many partly intimate features of an individual and may be misused against its interests in such fields as social insurance, work, marriage and family relations, estate inheritance and other social institutions where physical, intellectual and spiritual properties of an individual are so important. Genetic prognostications have a probability character, but may be used with malicious intents to suppress and exploit individuals. Anyway we cannot be certain whether people benefit from knowing their future.

Therefore the genetic portrait of an individual should apparently be considered as his/her exclusive and confidential property. The altitudes of Soviet scientists towards the programme of Human Genome studies is governed by humanistic moral-ethic standards placing top priority on individual rights and public benefit. These will become a subject of legislation to be openly discussed in public in this country.

THE HUMAN GENOME PROGRAMME IN THE UNITED STATES

Norton D. Zinder

The Rockefeller University, New York (USA)

ABSTRACT

In the United States, the Human Genome Project is a well-established, specific large-scale reality, with prospects for future expansion and clear aims that define it: high-resolution mapping of the Human Genome; complete sequencing of the human DNA and of model biological organisms; a physical map of human chromosomes and that of models; the creation of computer programmes and high-technology, high-capacity and development data-bases.

In order to follow through the programme and its aims, certain scientific procedures to be followed have been drawn up, which could be periodically modified in the light of the discovery of new technologies and of experimental result.

THE HUMAN GENOME PROGRAMME IN THE UNITED STATES

Norton D. Zinder

The Rockefeller University, New York (USA)

ABSTRACT

While we have already heard from speakers discussing the Genome Program from a number of countries, they've devoted most of their presentations to ethical issues. Since both Dr. E. Jungst, Director of the Ethical, Legal, Social Implications of the Human Genome Program of the U.S. and Dr. Nancy Wexler, Chair of the N.I.H. ELSI working group will be addressing this meeting, I'll talk mainly about the Genome Program of the U.S. I just note that a very large ELSI program is built into the genome efforts of both the N.I.H. and D.O.E. and will be funded at approximately 5% of their annual budgets. It is probably where it belongs for in this way it is fully integrated and stays coordinated with the scientific endeavors.

I want to assure the philosophers and ethicist in this group that there is a substantial scientific genome program both on going and being further developed in the U.S. today.

We consider the Human Genome initiative to be a world wide effort to map and sequence the entire human genome. The Human Genome consists of 23 pairs of chromosomes each containing between 50 to 250 megabases of DNA. The total Human Genome is 3x10(9) base pairs of DNA. These molecules contain some 100,000 genes which code for specific proteins. The structure of the genes, which are alternating sequences of coding DNA (exons) sequences and of non-coding sequences, (introns) is such that only about 5% of DNA encodes protein. Transcriptional units that include both exons and introns are, however, very large and are reduced to messenger RNA by RNA splicing. Thus, the gene, for example the gene whose mutations cause cystic fibrosis contains some 250,000 base pairs of DNA of which only about 4500 are coding.

When in the late seventies and early eighties techniques for manipulating and sequencing DNA became so efficient that several scientists envisioned sequencing the entire Human Genome. After about four years of discussions and workshops culminating in a positive report from the National Research Council, a joint program of the Department of Energy and the National Institutes of Health was established to accomplish this goal in the U.S.

The NIH's program is mainly an extra-mural one and is currently funded by the U.S. Congress at about $60,000,000 for FY90 and $88,000,000 for FY91. The DOE program is primarily an intramural (about $46,000,000) one at Lawrence Livermore, Lawrence Berkeley, and the Los Alamos National Laboratories. Working together, the DOE and the NIH Advisory Committees have put together a five year plan of action for the U.S. Congress. The plan is to be used primarily a guide and will be revised annually on the basis of new technological and experimental results of science. In this area, as in most areas o science, any attempt to set specific plans are overtaken by events. For example while the NCR report was written only three years ago, two techniques

that are now very important were not even discussed, that is the polymerase chain reaction (PCR) and high resolution *in situ* hybridization. Since, as noted below, one program goal is to stimulate new technology, developments events may even more faster. For example, PCR at the 100 kb level would revolutionize the approaches to the problem.

The program goals are:

- construction of a high-resolution genetic map of the Human Genome;
- production of a variety of physical maps of all human chromosomes and of the DNA of selected model organisms, with emphasis on maps that make the DNA of selected model organisms, with emphasis on maps that make the DNA accessible to investigators for further analysis;
- determination of the complete sequence of human DNA and of the DNA of selected model organisms;
- development of capabilities for collecting, storing, distributing, and analyzing the data produced;
- creation of appropriate technologies necessary to achieve these objectives.

Another program goal is to provide, from the outset, the means by which the public can be made aware and have input into the consequences of the legal and ethical implications of the findings.

It is currently assumed that the goals can be achieved in about 15 years with the clock starting at Oct. 1, 1990 (FY 91). Some $200,000,000 (1988) a year will be required. The exact expenditures necessary in the U.S. will depend in part on the activities of the rest of the world. Significant activity outside the U.S. will both shorten the time needed and reduce the proportion of U.S. expenditures.

A seat of five year Scientific Goals have been established as a way of proceeding:

Quote

1. Complete a fully connected human genetic map with markers spaced and average of 2 to 5 centimorgans apart. Identify each marker [whenever possible] with an STS. [STS, sequence tagged sites. For any DNA fragment 300 bases from one end are sequenced, twenty nucleotide oligonucleotides are made for each end of the 300 bases and by PCR the frag-

ment verified. This would allow all fragments to be stored electronically by sequence and make superfluous large and expensive collections of biological DNA clones. It thus provides a sigle language for describing fragments made in any laboratory at any time].

1a) Develop techniques for producing tissue specific and developmental stage specific c-DNA libraries with equivalent concentrations. Convert c-DNA isolated in any laboratory into STSs.

1b) In two to three years develop an index map of about 300 makers approximately 10 megabases apart for all chromosomes of the Human Genome.

2. Assemble STS maps of all human chromosomes with markers at approximately 100,000 bases pair intervals. Generate ovelapping sets of cloned DNA or closely spaced unambiguously ordered markers with continuity over lengths of 2x10(5) bp.

2a) Determine in regions of 2x10(6) bp all possible coding genes.

3. Improve current methods and/or develop new methods for DNA sequencing that will allow sequencing for $0.50 per bp [or less]. [Large scale sequencing decision for human DNA to be made at 4 to 5 years out].

4. Prepare a genetic map of the mouse genome based on DNA makers. Start physical mapping of 1 or 2 chromosomes.

Sequence an aggregate of about $20x10^6$ bp from a variety of organisms focussing on stretches that are 10(6) bp long [Model organisms are *E. coli,* yeast (*S. cerevisiae*), *D. melanogaste, C. elegans* and the lab mouse].

5. [Utilize a "Joint Informatics Task Force", DOE & NIH] to:

Develop effective software and database designs to support large-scale mapping and sequencing projects.

Create database tools that provide easy acces to up-to-date physical mapping, chromosome mapping, and sequence information so as to allow ready comparison of the data in these several STS.

Develop the algorithms and analytical tools that can be used in the interpretation of genomic information.

6. Develop [through a joint NIH-DOE working group] programs [research grants, workshops, town meetings, educational

materials] addressed at understanding the ethical, legal, and social implications of the Human Genome Project. Identify and define the major issues and develop initial policy options to address them.

7. Support research training of pre- and postdoctoral fellows starting in FY 1990 (up to 600/year, steady state). Examine needs for other types of training.

8. Support innovative and high risk technological developments... to meet the needs of the Genome Project.

9. Encourage and facilitate trasfer of technologies and of medically important information to the [relevant] communities.

Unquote

Currently the NIH program is supporting more than about 150 grants in all of the above areas. In FY90/91 we are establishing up to nine research centers with 20-50 persons focussed on genome research; to reach 10-15 centers in the next 5 years. The DOE supports the physical analysis of chromosomes 16, 19, and 21 at three National labs. In addition technologies such as scanning tunneling electron microscopy of DNA, laser detection of DNA and studies on a variety of database structures and tools are being supported.

Each center will have an outreach program. Facilities will be made available for doing lay scale mapping, database and software updates and exchange of information. The centers will thus serve as a way to partially decentralize management of the program.

Two questions are almost always raised. The first, whose genome will be mapped and sequenced? There will be no particular individual. Laboratories all over the world are studying different isolates of human cell lines, chromosomes and DNA segments. Those who will map and sequence will use their own favorite pieces. Thus, the map and sequences will provide a reference standard to which all other fragments form the same genetic region can be compared. For example, analysis of from 100 different people of specific 100 kilobase segments will provide detailed information of human variability. If a highly conserved region is studied, the comparison will provide insight into the evolutionary input of this region.

The other question is, why do it as a program. Two parts of the answer are given above. By focussed effort we more readily will derive deep understanding of human variability and evolutionary history. Many new genes of import will be ascertained including those producing disease. Given the sequences at anytime in the

future when a genetic problem arises, it will be simple to study the genes involved, more efficiently and cost-effectively than a present. Moreover a high resolution genetic map has great value even without the DNA sequence. When we translate all of the nucleotide sequences into proteins and then into gene functions, we will ascertain numerous important modulating and developmental proteins and therefore they'll be available for study and use. The major problem that we foresee is that we'll have genes before we have functions and therefore diagnosis of genetic diseases before we have therapies.

That is why we have established a large program relating to ethical and legal problems as an outreach to be sure the implications of the results are made clear to our relevant governors and the public. However, at bottom we must remember that our genome is a part of us and in large measure make us, us and therefore worthy of detailed study in its own right.

WHY ISOLATE THE THIRD WORLD? WHAT PART DOES UNESCO HAVE TO PLAY?

Claude Rosenfield

Adviser to the Direction of UNESCO, Paris (France)

ABSTRACT

The Third World covers most of mankind. The Human Genome Project is of an international nature and as such, demands the participation of scientist from all nations, including those form developing countries. On the other hand, respect for human dig nity and human rights is consubstantial to the Project from all points of view: ethical, religious or genetic engineering. UNESCO intends to promote international co-operation for Education, Science, Culture and Communication; it is therefore obvious that the result of research in agriculture, genetics or in other fields have implications for the whole of mankind and, in some cases, particularly for the Third World. There should therefore be no doubt about participation and exchange between developing and developed countries.

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ABSTRACT

The Third World covers most of mankind. The Human Genome Project is of an international nature and as such, demands the participation of scientist from all nations, including those from developing countries. On the other hand, respect for human dignity and human rights is consubstantial to the Project from all points of view: ethical, religious or genetic engineering. UNESCO intends to promote international co-operation for Education, Science, Culture and Communication; it is therefore obvious that the result of research in agriculture, genetics or in other fields have implications for the whole of mankind and, in some cases, particularly for the Third World. There should therefore be no doubt about participation and exchange between developing and developed countries.

Considering the potential public impact of the Human Genome Mapping and Sequencing Project, it is impossible not use the adjective Promethean to describe it. As the most prestigious product of the possibilities opened up by *genetic engineering*, it calls for the involvement, to paraphrase François Gross [1] not only of philosophers, "theologicians", jurists, legislators and politicians but also of men and women generally.

The remarks of the philosopher Michel Serres [2] may usefully be applied to the subject: "the third area of ethics focuses on the transition from potentiality to existence. A matter of divine decision in the classical age, a natural mechanism operated blindly by nature or by time since Darwin, a responsibility entrusted increasingly to ourselves since we fisrt began to intervene actively in the world –no doubt since the age of *homo faber*– it has suddenly become a much greater burden since we acquired the capacity to create possible worlds. On this matter we are no longer divided, be we philosophers, scientists, jurists or politicians. Whether we see it as taking part in God's councils of old or in nature's sowing of seeds, it may be within our power tomorrow to shape the world for the best".

These remarks sum up the reasons why it is not possible to exclude form this apex of knowledge, judgement and decision –taking qualified representatives of the majority of humankind: the Third World. Unesco's role is to facilitate exchanges of knowledge between the rich minority and the poor majority in order to prevent the injustice of the majority's being subordinated to a few, an injustice that is dehumanizing, "anethical" and antidemocratic, generating envy and hatred among those who happen by lack of resources to be reduced to passivity and impotence.

The role scientist from developing countries can play in the Human Genome Project, with Unesco's assistance, has been summed up by J. E. Allende of Chile [3]: "Most scientists agree that it is highly desirable that the Human Genome Proyect be a truly global undertaking, open to participation by scientits from all nations, including the developing countries. It also seems logical that Unesco, entrusted by the world community with the charge of promoting international co-operation in science, education and culture, should make efforts to facilitate the participation of the developing countries in this programme. The question is how.

My proposition is that such participation would be greatly stimulated by bringing together to small communities of human geneticists of Third World regions for the specific purposes of generating realistic regional programmes that would incorporate them an their countires into the Human Genome Project".

However, the issue is one that transcends the scope of science. In a world first invented and discovered by human beings before being fashioned by them science is no more than the most pow-

erful tool available to attain their goals. The Human Genome is the mythical and ultimate culmination of this search for the secrets of life, and it is particularly important that the instruments and findings of that search be regarded as the common heritage of humankind, of which no one must be deprived.

The scientists are fully aware of this fact and are anxious for it to become a public issue. In their report to the President of the French Republic in 1979, for example, Professor Jacob, Professor Royer and Professor Gros wrote: "Contrary to what some would have us believe, it is not through biology that a certain idea of human beings can be gained. On the contrary, it is in the light of a certain idea of human beings that biology can be used in their service". [4] "What a type of answers have biologists to offer, as biologists, to the question they are today being urgently asked by ordinary citizens and decision-makers?" [5].

Federico Mayor, at a Unesco symposium held at the Trieste Institute of Human Rights (whose Director is Guido Gerin), pointed out in connection with the relationship between genetic manipulation and human rights: "Genetic manipulation, in its broad sense, has many potential implications for human rights as it may have unforeseeable effect that can infringe the human rights not only of the child but of all his or her descendants ... Concerning research, its risks should be carefully considered in order to avoid inadvertent effects that may impair human rights ... The requirements of human dignity are the roots of human rights. Everybody should be able to develop his or her potential as fully as possible" [6].

With regard to this concern felt by scientists to ensure respect for human dignity it may be appropriate to quote paragraph 1 of the Valencia Declaration on the Human Genome Proyect, which incidentally also calls for public discussion of the issue and the specific participation of all countries: "The members of the workshop believe that knowledge gained from mapping an sequencing the Human Genome can have great benefit for human health and well-being. Towards these ends, participating scientists acknowledge their responsibility to help ensure that genetic information be used only to enhance human dignity. They also encourage public debate on ethical, social and legal implications of the use of genetic information. The members endorse the concept of international collaboration for the project and urge the widest possible participation of countries throughout the world, within the resources and interests of each country" [7].

It is clear that the concepts of *human rights* and *human dignity* in connection with the Human Genome and genetic manipulation are of concern to religious thinkers and jurists seeking to engage in a dialogue with scientists. For example, in her article entitled "Genetic screening, from newborns to DNA typing" Bartha Knoppers concludes: "in the context of the new genetics, the

assurance of and respect for human dignity cannot be limited to a conception of natural rights of the person that determine the genetic immutability of humankind and of the individual at birth, nor to a single right such as that of inviolability, or privacy, or indeed liberty. Respect for human dignity means that it is essential to talk not in terms of genetic rights but rather in terms of protection of the genetic heritage, of individual control over and access to the Human Genome, and of duties and collective responsibility in regard to it. Such an approach should serve as a source or appreciation of the specific, intrinsic value of each human being as such, for the individual in his or her genetic make-up and human nature and for the collective attainment of such 'humanitude'" [8].

The council of Europe, in the 1989 report of its *ad hoc* expert committee on the progress of the biomedical sciences (CAHBI) in the field of artificial procreation, stressed the fact that "the essential basis of human dignity is that all human beings are equal and that everyone had his or her own intrinsic worth". The human being must not be regarded as "a means" or as "an object". The principles put forward are aimed at ensuring recognition of the essential concept of human dignity and human rights as embodied in the European Convention for the Protection of Human Rights and Fundamental Freedoms [9].

In the reports quoted by Bartha Knoppers [10] produced by various North American scientific bodies on gene therapy and on the use of human genetic material, such respect for human dignity, "although little mentioned as such, is perceived as an individual and subjective concept [11]. Complementing this notion of human dignity, as a guarantee of individual subjective rights, is that of the inherent dignity of humankind, of the community, and the requirement to respect such dignity as the foundation of any truly human society. This latter approach is particularly evident in recent studies produced in France, the Federal Republic of Germany and Switzerland [12]. These three countries have begun to regard the survival of the dignity of humankind as part of the protection of the human species as a whole. A report by the French Government and a recent draft law have given renewed expression to the overall concern regarding the limits on the freedom an individual may exercise in deciding the fate of his or her gametes or embryos and the future uses to which they are put". In accordance with that view, "individuals are free to act as they choose but they are also accountable to others and to themselves and hence may not attack humankind through their own persons. Accordingly, no action that is incompatible with human dignity and that prevents the individual from developing and fulfilling his or her human potential can be permissible" [13]. It is of course not possible to report here all he discussions that are summarized in the excellent sypnotic article. I shall confine myself to quoting, in regard once again to Unesco's role, that played by the different nations for and through their citizens and the need to take

acoount in discussions of all the cultural, moral and religios factors involved in order to enable decision-makers to be guided by the principles emerging from the scientific debate, the following paragraphs: "Even assuming that, at a societal level, the protection of the common genetic heritage of humanity and the necessary genetic responsibilty towards future generations take the form of the banning at national and international levels of the two extreme positions, namely genetic manipulation for non-therapeutic purposes and eugenic applications, the postulate of human dignity in its clinical application in human genetics requires 'a preference for persuasion rather than coercion' ... the future of human genetics lies not in the obvious controversies surrounding manipulation or elimination but rather in the communication of genetic information in genetic education and in the making of informed genetic choices..." For "the pursuit of human dignity as a goal consists in seeking the means of reducing human affairs to laws that maintain the greatest possible liberty" [14].

In order to preserve what is uniquely human, to prevent the loss of what is sacred, to ensure that the human body or its constituent parts or even its cells themselves do not become commercial products or research materials used in non-therapeutic scientific experimentation, it is essential that human rights should exercise their new function of "mediating between ethics, the law, and politics, thereby enabling a dividing-line to be drawn between what is just and what is unjust, and aimed at establishing what might be termed... a legal identity having a variable content" [15]. The positions quoted above are not far removed from those of the Catholic theologian Klaus Demmer and the scientist Jean Dausset, whether speaking of the individuality or uniqueness of the human person from a religious, transcendental point of view or from the standpoint of genetic engineering.

According to Klaus Demmer it is essential within a pluralist society to reiterate the presuppositions of Catholic theology when dealing with problems of human genetic manipulation. "The key concept to which the ethical argument refers is reflected in the normative nature of the human person. It is in this concept that the thinking of the moral theologians is rooted: for *revelation* does not by itself provide a criterion that can be directly applied to the intramundane order, even if this does not mean that it cannot propose a general framework within which to develop the ethical discourse. In order to avoid all possible misunderstanding it should be added that this framework consists of a series of elements structuring a comprehensive Christian anthropology that still remains to be worked out and analysed ... At the core lies the dignity of the human person in so far as it is a relationship to God... What must be borne in mind here is the individual, unrepeatable nature of the history of each human being, and the protection that must accordingly be given to his or her personal identify throughout that person's existence ..." [16].

These postulates enable Demmer to write further on: "The conviction is beginning to permeate contemporary theological thinking on moral issues that action to modify the genetic code is legitimate when the intention is strictly therapeutic ... Years ago Pius XII took a favourable view of the contemporary prospects opened up by negative eugenics designed to eliminate hereditary diseases ... The doctrine of the present pope follows much the same lines, ... explicitly approving the use of genetic engineering for therapeutic purposes."

Emphasis, however, is placed on problems relating to prenatal diagnosis of genetic disease: "In accordance with the principles that are valid for all forms of diagnosis, the morality of such diagnosis is contingent upon the motivation of the person asking for and the person undertaking the diagnosis, and upon the goal aimed at. What nevertheless poses a problem from the moral standpoint in the selection of embryos and foetuses for eugenic purposes, if in the event of an unfavourable diagnosis a termination of pregnancy is desired or require".

Klaus Demmer, in his conclusion, remind us that the human being, through his or her scientific conquests, is a co-creator and hence God's collaborator. He also calls for an interdisciplinary dialogue, with jurists among the participants, in order to achieve a consensus and to prevent dangerous abuses.

This concept of the unqueness of the human person is further recalled at the biological and genetic levels by Jean Dausset: "With each generation therefore are born beings –products of the genetic lottery– that are new and unique inasmuch as they are formed of entirely new combinations of genetic characteristics" [17].

Thus there are points of agreement among people of the same culture, be they scientists, religious thinkers, philosophers or jurists, concerning the unqueness of the human person and the permissibility of modifying the Human Genome for a therapeutic purpose limited to that single (and unique) person, that is, an intervention affecting the somatic cells but not the germ cells. Beyond this, problems arise, and the definition of right and wrong relates to conceptual frameworks or experience that call for explanations, pooling of information and honest attempts to compare views.

For example, James Watson stated his position at the Unesco symposium held at the International Institute of Human Rights in Trieste (referred to above) in the following terms: "As a scientist I am hesitant to make sweeping generalizations as to the moral implications of our increasing mastery of DNA and the molecules that make life possible. Differences between right and wrong often appear more intuitive than deductive... As each of us possesses some hundred thousand different genes it is clear

that none of us possesses only 'good' examples of these genes. In some cases a given gene will always be bad, but in many cases the final effect will depend where and how we live. I fear, however, that many of us will no longer have this freedom to appear as non-controversial good guys ... We thus have no choice but to talk openly about these discoveries so that they can be seen as opportunities for further human advancement rather than as linchpins for the undermining of the Judaeo-Christian ideals that have so successfully promoted the development of Western civilization ... Much more difficult to resolve will be the question of whether selective abortion of genetically disabled foetuses should occur.

Here again, the heart of the problem lies in how we perceive human life *per se*" [18].

Quite recently, François Gros made the point, in a statement to the political decision-makers at the Meeting of European Ministers for Research on Bioethics, that "sciences that are concerned with genetics and reproduction directly challenge the individual and society and consequently arouse the interest of the politicians" [19, 20]. He gave four reasons for this, which I shall summarize as follows:

1. Genetic methods permeate all branches of biology, and the pace of progress in these fields frequently makes it difficult for the general public to understand and keep up with what is going on. "Hence it is a matter of communication and education as much as one of responsibility."

2. Biology has moved on from the contemplative stage to the analytical stage, and thence to that of intervention. Its applications now lie within the realm of the advanced technology.

3. The third reason lies in "the more or less conscious collective memory of totalitarian ideologies, in particular during the Second World War, relating to so-called scientific data that led to a form of eugenics raised to the status of a policy or system. Hence the fear that the new biology may serve once again to promot such designs remains very strong". This fear leads to positions being taken that are aimed at ensuring protection of individuals and their ethnic diversity.

4. "To all these reasons must be added those drawn from ecology in the broad sense". The biological sciences are suspected of paving the way for a new mercantile order in which it will be the turn of human beings to become consumer goods.

"For all these reasons a new chapter of morality, known as 'bioethics', has been opened."

With regard to *genetic engineering and the exploration of the Human Genome*, the document "Ethical issues involved in genome research prouced by the Standing Committee for Legal Affair and Citizens" Rights of the European Parliament assert that not all that is technologically feasible is necessarily desirable for the human species.

Concerning the exploration of the Human Genome, François Gross draws attention, after considering the advantages of and criticisms levelled at this project, to the *usefulness of adopting a concerted attitude at international level* in order to organize sufficiently rapidly the process of thinking about the individual and social consequences of such research, "so that it may be undertaken in optimal conditions, there by obviating undue and useless expenditure on redundant programmes and above all preventing the results of such research from being 'taken over' by dubious ideologies or for essentially mercantile purposes".

Among the ethical principle he mentions as being particularly useful, the following may be highlighted as relevant to Unesco's role: the establishment of an adequate number of data banks, a determination to ensure that biotechnology, agriculture, research on tropical diseases, etc. benefit from the methodological and technological spin-off such research, this being of particular interest to the Third World, and, finally, reflection on copyright and possibly rights of utilization in respect of genetic data on human beings in order to ensure that these become an inalienable international heritage, as indeed was already suggested at the last Unesco meeting [21].

These techniques for the study of the Human Genome, devised in the countries of "the North", concern –in so far as their future development, their results and their applications are concerned– humankind as a whole.

Nevertheless, it is clear from a perusal of the many works that have already been published that one of the major priorities is to establish collaboration with Third World countries on a sound footing.

The fact is that scientific information, and active participation in highly costly and highly competitive research projects and applications, are a matter of vital concern to the people of the Third World, who constitute the great majority of humankind. Such participation should make it possible both for the scientists of the countries concerned to be active partners in developing and extendig such knowledge and for the specific needs of those countries to be fulfilled.

However, if it is the biologists' task to decipher "the book of the human being", it is the theologians, the philosophers, the jurists, the legistlators, the politicians and indeed the public at large that

have the duty of discussing the issues affecting this common heritage.

Unesco, the interdisciplinary agency of the United Nations for education, science, culture and communication, which has over 159 Member States the majority of which are in the Third World, has received recommendations from the scientific community aimed at promoting and facilitating all aspects of international collaboration relating to the Human Genome –medical, technological, scientific and ethical– special prominence being given to its role in relation to the Third World [22].

On the basis of these recommendations, and following consultations with Member States and approval by the Executive Board and the General Conference of Unesco at their last sessions, the Human Genome Sequencing Programme was included in Major Programme Area II for 1990-1995. Its aim is to promote internation co-operation with the national, regional and international organizations concerned, both governmental and no-governmental, such as ICSU and HUGO, and thereby to facilitate participation and exchanges between developing and developed countries. Finally, a Scientific Co-ordination Committee, chaired by Professor Santiago Grisolia, has been set up to steer Unesco's action in this field.

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RELIGIOUS CONSIDERATIONS

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THE CATHOLIC POINT OF VIEW AND ITS ETHICAL IMPLICATIONS

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ABSTRACT

The Catholic Church recognizes the value of basic scientific research and gives great importace to progress derived form applied research in general and from the Human Genome Project in particular. However, the Church is against selective abortion which it fears will increase once pre-natal diagnosis facilitates the detection of a great number of genetic disorders. Likewise, it considers germinal therapy and in vitro production of embroys to be morally unacceptable. Nevertheless, it accepts genetic therapy in somatic cells and supports the approach of a predictive medicine designed to safeguard the family and population, even though it knows that this will generate conflicts between the right to freedom of choice on the one hand, and the rights of other programmes or communities on the other.

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The Catholic Church recognizes the value of basic scientific research and gives great importance to progress derived from applied research in general and from the Human Genome Project in particular. However, the Church is against selective abortion which it fears will increase once pre-natal diagnosis facilitates the detection of a great number of genetic disorders. Likewise, it considers germinal therapy and in vitro production of embryos to be morally unacceptable. Nevertheless, it accepts genetic therapy in somatic cells and supports the diffusion of a preventive medicine designed to safeguard the family and population, even though it knows that this will generate conflicts between the right to freedom of choice on the one hand, and the rights of other programmes or communities on the other.

As a human geneticist I have enjoyed the adventure of following, step by step, the rapid and extraordinary development of human genetics, from the formal level up to the molecular one, culminating now in this "big science" which is the Project of mapping and sequencing the Human Genome. All along, it has gradually become clearer to me that every progress has been accompanied by new responsibilities, due to the emergence of novel ethical and social implications. This is expected to occur at still higher rate when the Human Genome Project will be carried out. Therefore, all of the people involved in promoting such project, both in the scientific and administrative areas, repeatedly stress the need to take into consideration all the consequences of the inevitable increase of knowledge and its resultant power, as well as of the many foreseeable applications of the new findings.

The Catholic Church, like all other religious groups, is particularly sensitive to this urgency. She recognizes, and highly appreciates the intrinsic value of basic scientific research, and attributes great importance to applied investigation: indeed, as far as its religious view of the world is concerned, they "constitute a significant expression" of the "dominion over creation" which is entrusted by the Creator to man [1]. As the same time, however, she feels it as her essential duty that two tasks be accomplished: first, to examine all the aspects concerning human responsibility, both in the manner of acquiring knowledge, and in the applications that inevitably follow new discoveries; second, to help, through her teaching, first of all the catholics, and then all others who wish, to see what should be the right and consistent conduct in acquiring science as well as applying it. In the specific case of the Human Genome Project, the concern of the Catholic Church is not the Project itself. Well aware of her lack of competence in the area of experimental sciences, she trusts the experts who can evaluate the pros and cons of the Project, discuss the many problems involved in its execution from the scientific, political and financial standpoints, and decide about priorities [2-5], confident that a great amount of new and important knowledge will be acquired for the good of mankind. The Church's main concern is the use that can be made of this knowledge. I will briefly refer to three areas, that I deem of particular interest, where the new findings could be applied, and will outline the position of the Catholic Church on some ethical implications. I do this with sincere respect to all other points of view and ethical positions, which are expressions of different cultural outlooks, and deserve full consideration [6].

A first area in which the high-resolution mapping of Human Genome (which seems to be the first and nearest target of the Project) will have immediate effect is that of prenatal diagnosis of genetic diseases [7-12]. Other participants will deal with the scientific and technical aspects. I will simply mention that the number of deleterious genes for which either the homozygous or the heterozygous state could be detected at the embryonic or fetal stage,

or even prior to implantation in case of in vitro conception [13-16], will greatly increase, not with standing the many scientific, technical and logistical problems that remain to be solved. As a consequence, in the present state of knowledge, the number of cases in which the current policy of selective prenatal, or preimplantation, termination might be applied, is expected to raise considerably. This is, notoriously, a point of ethical tension [17-18]. The position of the Catholic Church is not of absolute condemnation of prenatal diagnosis [19]. However, according to her doctrine, prenatal diagnosis is good if "the life and integrity of the embryo and the human foetus" are respected, and it is "directed towards its safeguarding and healing as an individual". This position, that is clearly contrary to selective termination of fetus or embryo, is based on the following principle that she considers to be a fundamental one: "The fruit of human generation from the first moment of its existence... demands the unconditioned respect that is morally due to the human being in his bodily and spiritual totality... and therefore from that same moment his rights as a person must be recognized, among which in the first place is the inviolable right of every innocent human being to life". According to this viewpoint, the "quality of life" is certainly a great value, that science, medicine and society must strive to improve for and in every human subject; but it is not the man's right to establish at which point in the range of the "quality of life" one can dispose of an other man's "life".

A second area where progress in the knowledge of the Human Genome will open new perspectives is that of preventive medicine through carriers' detection and preventive counseling [20]. A good part of the Workshop is dedicated to this topic, and certainly the great possibilities, but also difficulties and problems, for the achievement of these goals will be presented and discussed. I shall only add that this line of approach, aimed at avoiding the conception of individual lives loaded with sufferance, and at preserving and promoting the quality of life of families and populations, by reducing the burden of genetic disorders, is warmly supported and favored by the Catholic Church. The engagement of science to discover the determining factors of many disrupting diseases; the endeavor of medicine to identify and responsibly advise subjects at risk, helping them in their decision; the efforts of society to create all the facilities for a primary preventive medicine, and for the indispensable education; and, finally, the care of the subjects at risk to reach mature personal choices, altogether constitute the solidarity that, in the view of the Catholic Church, should characterize a humane enterprise and should be the expression of true humanness.

In this large cooperation a number of ethical problems may arise [21-23], due chiefly to possible conflicts between individual's right to freedom of choice and privacy, on one hand, and other people or community requirements, on the other, as for in-

stance in the case of family or, even, population screenings. No general solution appears to be possible. However, in the light of the basic ethical principles of the Catholic Church, justice, equity, respect of the dignity of any human being, and true love must all be taken into consideration in the attempt to find a prudent and wise answer to every single problem in any single case.

A third area, where research will be accelerated by the achievements of the Human Genome Project is that of gene therapy [24-28], that shall also be examined in our Workshop. In accordance with the principles which are at the basis of the morality of therapeutic treatment and experimentation in humans, the Catholic Church participates in the general ethical consensus now reached for somatic cell gene therapy, that could even be extended to embryos with due respect for their life and integrity by avoiding disproportionate risks [29]. Yet, the fact that the Catholic Church [30] considers the production of human embryos in vitro, for whichever reason, to be a violation of human dignity, and therefore morally illicit, makes any type of germ-cell therapy involving the fertilization in vitro also ethically unacceptable.

I have simply proposed the essential teaching of the Catholic Church concerning a few ethical aspects implicated in the medical application of new findings of genetics, which are expected to grow and expand very rapidly under the powerful impulse of the developing Human Genome Project. Undoubtedly, one cannot avoid the impression of a rigorous and intransigent doctrine. This is probably one reason why not all catholics agree. However, it is only honest of me to quote a few sentences from the introduction to a recent pertinent document, from which one can perceive the spirit underlying that doctrine [31]. "The Church's Magisterium... having taken account of the data of research and technology, intends to put forward, by virtue of its evangelical mission and apostolic duty, the moral teaching corresponding to the dignity of the person and to his or her integral vocation... The criteria of moral judgment... are the respect, defense and promotion of man. The Church's intervention in this field is inspired also by the love she ows the man, helping him to recognize and respect his rights and duties".

To conclude: some of the statements I have made so far, representing the true teaching of the Catholic Church, probably will contribute to maintain the ethical tension that permeates the most advanced frontiers of human and medical genetics; a tension that can be felt as a disturbing force by those who are engaged in this field. However, it must be recognized that a great deal of advances in science in general, and in medicine and medical genetics in particular, always occurred in an atmosphere of ethical tension. The fundamental, hidden cause of this tension is, I believe, the existing, inevitable difference in the cultural backgrounds upon which individuals or societal groups

found their ethical principles of behavior. For this very reason the tension will not easily subside. But, perhaps, it can gradually lessen if we could succeed, as it happens in most fields of research, to make, out of the plurality of opinions, a matter of constructive, reciprocal understanding, so that basic and applied research might have a still stronger impact for the true well-being of mankind.

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ARTIFICIAL REPRODUCTION: AN ISLAMIC POINT OF VIEW

Azeddine Guessous

Moroccan Ambassador to Spain

ABSTRACT

The position of Islam is to support science and scientific development by encouraging man to acquire greater knowledge in all fields. However, based on the commandments of the Coran –the Sacred Book of Laws which governs all activities of Muslim men– Islamic theologians categorically reject any form of artificial reproduction that uses the sperm of a donor who is not the husband, as likewise any that brings about the destruction of the embryo.

Muslim moralists consider that science has to coexist alongside religion and ethics and believe that its multiple applications should be controlled. To be more precise, they support a moratorium of genetic engineering and artificial reproduction as applied to man.

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Muslim moralists consider that science has to coexist alongside religion and believe that its multiple applications should be controlled. To be more precise, they support a moratorium of genetic engineering and artificial reproduction as applied to man.

I am very much honoured and delighted to have been invited to join in this important gathering the International Cooperation for the Human Genome Project.

The reputation of the "Fundación Valenciana de Estudios Avanzados" is already well known and well established and on this ground alone, it is a privilege to present a paper here.

The theme of our symposium interrogated every man's conscience: scientits, physicians and biologists in particular, political men and populations concerned, it interrogates the conscience of the religious families. Not being a formal delegate of any muslem community and not being a specialist in muslem theology, I shall limit myself to the ethical aspects related to artificial human procreation, seen from the point of view of Islam, knowing that it represents only an aspect of the very wide theme which is submitted in our reflexion. But it is a fact that islamic scholary have not welcomed artificial forms of procreation whith a great deal of enthusiam. What is the explanation of this negative attitude?

But first, let us see the islamic attitude towards science and scientific development

Islam does accept the theological doctrine of natural law, that to say the theory that affirms that the universe and, more generally, nature, is designed by God for the fulfillment of specific goals. Islam believes that intelligence is evident in the laws of nature and that creation is designed for a purpose. But Islam rejects the notion contained in the doctrine of natural law that man should not, thanks to his skill and intelligence, transform nature and act upon to in order to improve human condition.

In the name of this principle, one could oppose any intrusion of human knowledge in the determination of the living. On the contrary, Islam, as from the beginning, has been in favour of antibiotics and surgery. Islam is for the progress of science that can cure sterile couples, prevent anomalies, fight spontaneous abortion or the risks of prematured abortions. Never, even at the very beginning of the caesarian surgery, Islam opposed its practice on women. Islam encourages man to seek more knowledge in all fields and places the scientific in a special level of diving considerations. A verse of the Coran says "How can these who know and those who do not know be equale?".

So Islam denies the notion of natural law which legislates against the thwarting and manipulation of nature. Since Islam encourages science and scientific developments and since there can be not opposition on grounds of natural law, why this reserve towards artificial forms of procreation?

It has to be reminded that although islam interpretations are not monolithic and that within Islam there are different opinions with

regards to many issues among scholare (ulémau), this religion in first and above all a religion of law. As such, the basic principle is that if the Coran does not proscribe any act as a contravention of divine prohibition, then the action is permitted or, at least, not condonnable.

What are then the grounds for the negative attitude of Islam towards the most critical of the new techniques, that is to say the *in vitro* fertilization of ovum and sperm and the replacement of the embryo thus engendored in the uterus of an otherwise childless wife? Part of the answer lies in the primacy of the value of the family and family ties in islamic conception, Islam has always had the highest respect and the highest consideration for the integrity of the family. But one can point out that the promotion of family values is of great concern to moralists of various religions throughtout the world and consequently is not a monopoly of Islam.

In many verses of the Coran, Adam is ordered to procreate and this commandment is specifically directed to him, that is to say: the male.

The divine imperative is consequently a commandment to engage in sexual activity within the marital framework with enough frequency until children are conceived. Thus, the essence of the divine commandment is the sexual act itself and the only act which is ordered is the act which is natural. The only mandated form of procreation is that which stems directly from sexual union.

As far as artificial forms of procreation are concerned, they might, at least in the narrow legal sense, be regarded as permissible unless a violation of some specific divine commandments is committed. And it is a fact that some forms of artificial procreation do transgrede the limits precisely defined by the Holy Book.

Insemination of a married woman with the sperm of a donor other than her husband

The main reason to the opposition of Islam to this form of artifical procreation is not the transgression of marital obligations as there is no sexual prohibited intercouse between the donor and the woman. And the sexual act in all theological systems is defined as penetration. What motivates Islam posture is its commandment against adultery. And the prohibition against adultery is based upon the necessity that paternal identity be absolutely certain, without the least ambiguity, least progeny, unknowingly, have incestuous relationship.

And the insemination of a married woman with the semen of a donor might lead to incestuous relationship. That is why, according to the overwhelming majority of Islam theologists, the utilization of the semen of a male other than the husband to inseminate a married woman is pure and simple adultery. That is why this religion categorically rejects any form of artificial procreation which involves the introduction of semen other that the husband's into the genital tract of a married woman.

Destruction of the zygote

The *in vitro* fertilization implies a second serious problem which derives from the destruction of a living embryo. As a matter of fact, everytime an ovum fertilized with the semen of the husband is implanted in the uterus of his wife, there does not arise a problem, from the theological point of view. The problem arises when a certain number of ovum are simultaneously fertilized, and some of them are not implanted in the mother's uterus. What will be the destiny of these ova? Killing a life, even that of a foetus, is totally prohibited by muslem religion. To take somebody's life, even that which man has contributed to create and could not have existed without his skill and knowledge, is criminal.

The question is when does the fertilized ovum begins to be considered as a human being? Here, the opinions differ and we continue no attend a on-going debate and disagreement among moslem scholars.

A school of theologist headed by Abdallah Guennoun, taking ground on a versus of the Coran which considered that man bears inside himself his progeny, has gone so far as to affirm that life is in the semen and the ova before the phenomenon of fertilization takes place.

At the other extreme, others consider that the embryo becomes a human organism only when it becomes visible to the naked eye and consequently, the law does not give it a legal recognition when the organism is still sub-visual.

The difficulties to identify the moment when the human organism is formed, as from the moment of fertilization, have led other moslem scholars to recommend that all fertilized ova should be introduced into the wife's uterus and if this is not medically acceptable for reasons related to the mother's or the foetus' health, they suggest to take from the woman only the number of ova than can be safely reimplanted once artificially fertilized.

The conservative moslem theologists claim for the embryo, from the time of coneption, the same status and therefore the same fight to protection as in due to all human beings throughout life.

They, therefore, absolutely prohibit the taking of "innocent" embryos life, no matter what the estimated benefit either to a third party or to medical progress in general. Because of its genetic potential to become a human being or a human person, the embryo must be treated as though it actually ware one from the beginning.

Another fundamental motivation that supports the reserve of Islam with regard to *in vitro* fertilization and other forms of procreation experiments is the principle that order us "to do no harm".

Man is not morally entitled to create life in order to inflict harm or injury upon the bearer of that life. For Islam, all experimentation upon unborn foetuses is immoral and unethical.

Such experimentation is unethical because it is impossible to predict whether it will result in the birth of a defective child who, otherwise, would not have been born. Life should not be artificially generated when such generation carries with it the risk of suffering or pain.

Date relative to the congenital defects in the thousands of births which resulted from *in vitro* fertilization are not available and little information about it has been published in medical literature.

But it seems reasonable to think that, at least in the first period of the use of *in vitro* fertilization, the birth of defective children had to be anticipated.

The simple physical manipulation of the ovum and the zygote and the reinsertion of the developing embryo in the mother's uterus could have resulted in genetic accidents. On the other hand, for moslem scholars, the fact that the fertilized ovum remained, even for a limited time, outside the uterus could have prevented the intervention of mechanisms employed by nature, specially at the early stages of gestation which are aimed at eliminating defective foetuses.

Defective children might have been born. They would not have been if artificial techniques had not interfered with the natural process of gestation.

As a matter of fact, the history of medical development is full of examples of unethical acts which, later, have led to substancial benefits for men and, most probably, this will also be the case for artificial procreation. But what makes the *in vitro* fertilization manipulations suspicious to ethics is that they are applied to the very creation of human life and that any error can result in irreversible damage to the foetus.

Because of the short time that is allowed to me, I cannot tackle other aspects of certain forms of artificial procreation which motivate the negative attitude of Islam, such as:

- The impact upon the child when he learns the technique used in generate him or once he learns he is not the biological son of his parents.
- The fact that *in vitro* fertilization seems to result in the preponderance of female births over male births.
- The possibility, in the future, to pre-select the child's sex or a specific genetic character. These are areas in which legislations have to be promulgated in order to avoid social evils that might threaten the structures of our societies.

Conclusion

For moslem moralists, science with its multiple applications should note be left to itself. As the water of the torrent that goes down for the mountain, it can ruin and death, it has to be canalized and oriented towards specific objectives.

The genetic engeneering and the very techniques of artificial fertilization, if applied to agriculture and breeding and put at the service of a world-wide development, instead of being the monopoly of a few countries, could contribute to better the condition at "all men and all the man", as said His Holineus Paul VI.

The moslem theologists consider that science has to go on being, along with religion and ethics, a basic factor of progress and universal peace, between men in all continents, who do not need additional inequalities, yet need, on the contrary, a deeper and more visible solidarity.

They join their voices to that of those advocate a moratory in the field of genetic engeneering and artificial procreation applied to man. This invitation, although only expressed, is a sign of wisdom which deserves to be scrutinized at least as carefully and with the same preoccupation as the production and experimentation of nuclear arms.

As said the professor Testart, pioneer in the IVF, a moratory in the investigation in human *"in vitro* fertilization" is necessary because it carries the risk to lead to a radical change of the human person.

One should not forget the centers of conservation called "embryos' bank" certain or will contain a great number of potential human beings, a whole population in expectation of life. It should not be allowed, under any pretext, to have humanity stored in diplicate, to make human reserves that can be used for God Knows which purposes. This should induce us, whatever the religion we belong to, to advocate the promulgation of a specific leg-

islation. Possibilities exist in a short future to multiply identically the same individual (and this is called cloning) to create new especies and predetermine individuals (and this is genetic manipulation). Who cannot see that it is absolutely necessary, if we wish to preserve man in his singularity, to set up barriers against these great dangers. The law, here, should play fully the protective role it is made for.

ETHICAL ATTITUDES OF A JEWISH SCIENTIST WITH REGARD TO GENETIC INTERVENTION

Haim Aviv

President of the Aviv Investment Company and Associates, and of the Pharmos Company

ABSTRACT

Knowledge of the human genome and the possibility that this information be used to modify human genetics pose certain ethical problems. The fact that creation is not perfect opens the door to man to intervene with the aim of perfecting, but never harming it. If God created one sole man in His own image and likeness, the concept of genetically inferior races is irrational. In this sense, knowledge of the human genome will clearly show the equality of human beings.

As far as genetic therapy is concerned, its application to somatic cells is no different to other therapies. However, the genetic intervention of germinal cells requires a somewhat more complex analysis.

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Let me start by telling you that I am not in any way a rabbi or theologian. I have a long interest in Jewish studies and tradition. The following are my personal thoughts on the subject as a Jewish scientist. They are based on my understanding and interpretation of Jewish tradition and philosophy. To some extent they are also based on certain legal discussions. These thoughts do not, however, constitute a formal legal opinion on Jewish law ("Halacha"). Let me also add that in the good tradition of Jewish culture, one can find opinions which are different from mine, but I believe that these remarks that I am going to share with you are in line with Jewish tradition and philosophy. With great reluctance and hesitance did I undertake to share these remarks with you.

Let me outline the problems and issues that I am going to discuss: Detailed knowledge of the Human Genome and the techniques and possibilities of using this information to intervene genetically in the human genetic make-up present at least three main ethical/theological problems:

1. Knowing the detailed Human Genome, may reveal information that supports the notion that certain races are genetically inferior to others, thus causing racial discrimination.

2. Genetic intervention in "God's Creation" is an arrogant human act. Using gene therapy is "playing God" and should not be practiced.

3. The techniques of genetic manipulation can *potentially* be misused to harm and to damage creation. They, therefore, should not be developed at all.

I will discuss these issues first on a philosophical level, and then on a somewhat more legalistic level.

Philosophical approach

The Jewish attitude is that Man plays a central role in the world. Man is the "crown" of creation. As the book of Genesis puts it: Man was created in God's image. Furthermore, without Man, God's kingdom in the universe is limited. Man is an important *partner* to God. Many Jewish philosophers share the opinion that creation is, in fact, not perfect. This is a very interesting concept. The Almighty has left things for Man to complete, perhaps purposely.

This places very important responsibilities on Man. Man should be a responsible partner and behave accordingly. In my opinion, there is nothing wrong with "playing God" if it means improving Creation and if it is done in a responsible way as a good partner.

Man has to work as a partner with the Almighty in order to perfect His creation and to avoid causing it harm. As Man is central, so is his life, his health, his well-being, and dignity. Saving human life is one of the highest priorities in Jewish law, superceding most other laws. Healing and reducing human suffering are considered means of helping and caring for God's image. Rabbi Moshe, the son of Maimon known as Maimonides, the great Jewish scholar, philosopher and physician, who was born in Cordova (1135 AC) and later fled with his family from Spain, wrote 800 years ago: "A healthy body in God's will, because one cannot know and understand God if one is sick. Therefore, one should avoid things which are harmful to the body and should behave and do things which promote well-being and good health".

Jewish philosophy does not assume an "Original Sin" that needs to be dealt with. We believe that Man can potentially be very elevated and close to God. "And You have made Man a *little* lower than God" (Psalms). The Kabalistic Messianic concept is that at the end of time, Man will achieve a high moral status. Creation has a positive direction. Man, through his behaviour, has enormous power to accelerate this process. This is a very positive and *optimistic* approach. I may go as far as saying that using modern genetics to better understand Creation and to improve Creation is what the Almighty expects from us.

Specific issues addressed

1. Genetic Information

As the world is God's creation, knowing creation is a way of knowing God and perhaps better appreciating Him. Knowledge of creation is, therefore, highly desirable. The concept of *genetically* "inferior" races is obviously improper and unreasonable. The book of Genesis tells us that God created only one man (Adam). Jewish commentators asked: Why did God create only one man? In order to teach us that all mankind is equal. Maimonides wrote the following: "... And Adam was, therefore, created alone in the world, to teach that ending a single life is like ending a whole world, whereas saving a single life is like saving a whole world... and every person can, therefore, say and feel that the world was created for himself." According to Genesis, Eve was a somatic clone, not even a different genetic organism.

I predict than once the Human Genome is completely known, it will show how remarkably equal human beings are and there will not be a *scientific* basis for racism based on intellectual or behavioral genetic differences.

Two aspects of gene therapy will be discussed, somatic therapy and germ line therapy.

a) Somatic Therapy

In my opinion, this is in essence not different from any other therapy, it is very positive and desirable. This is just a long-lasting therapy. Live vaccination is also a long-lasting therapy. Healing sickness can be a life-saving act and is, therefore, long lasting. Elimination of suffering is greatly desirable. Although sickness and suffering can also be viewed as a punishing signal from God, man should nevertheless do everything he can to reduce human suffering and to preserve human life. Preservation of life, saving God's image, is one of the most important commandments and supercedes almost all other commandments. Maimonides wrote: "If one becomes sick and may die, and the physicians say that his recovery requires doing something which is forbidden by the laws of the Torah, we are permitted to do everything, including that which is usually forbidden, except for three things (one of which is killing another person).

As in any other form of therapy, the proportion between benefit and risk should be evaluated. No obvious harm should be done, of course. The Jewish approach is to evaluate the risk/benefit ratio vis-a-vis the *individual patient*, not in generalities. The physician has responsibilities towards the individual patient in question. There is less concern in terms of "potential" harm. When immediate help to an individual is contrasted with *potential* long-term damage, immediate help, particularly that which preserves life, takes priority according to Jewish law.

b) Germ line intervention

This may be perhaps a more complex issue. This is a very long lasting therapy which will influence generations to come.

I believe that, in many ways, this is also not too different in essence from other therapeutic approaches that we are taking.

Treating infertility problems, for example, is a long-lasting intervention which will greatly influence generations to come. Life saving can have long-lasting effects in generations to come.

On a more technical/legal level, the manipulation of embryonic cells and embryos may present problems by endangering the "life" of the immediate, individual embryo.

The Jewish approach does not define the embryo as a living individual during the first month (or 40 days) of gestation –it is a special tissue. Therefore, according to Jewish law, this is not a major obstacle to genetic manipulation. In fact, up to the moment of birth, the embryo is not legally defined in the same way as a living human being in the context of murder, for example. I must, however, emphasize that according to Halacha, terminating pregnancy without a good reason should not be a normal practice. On the other hand, it is not considered murder for legal purposes.

The view, held by some, that we should not even develop the technology of gene manipulation because this technology may be exploited and misused in the future is very pessimistic and is not consistent with our attitude and basic trust in Man. We assume that Man is originally good, and that he can, and will be, even better. Of course, we have to watch and set up rules and fences to avoid the misuse of knowledge. The very fact that meetings such as this take place raises consciousness and awareness of the problems.

Technology, in principle, is neutral. The *way* in which technology is used by Man determines whether or not it is good or evil. Rabbi Moshe, the son of Nachman (Nachmanides) (1194-1270), another scholar and physician who lived in Gerona and also fled from Spain 750 years ago, commented in his interpretation of the book of Genesis (in relation to Lemech, presumably the inventor of metallurgy) that building swords is not a sin but killing is a sin.

Interestingly, Nachmanides also wrote that a physician who knows to heal is obliged to heal, and if he avoids doing so, he will be viewed as shedding blood. Drawing this statement to a logical conclusion, it means that if a physician knows how to cure a disease by genetic means, he has an obligation to do so without any delays.

In conclusion, the challenge is to guide and teach our communities and indeed all mankind to be responsible and to adhere to moral values in general. We hope that our basic optimism and belief in Man, who is created in God's image, will be justified. Being created in God's image is a great honour but also carries with it the utmost responsibility. The Kabala which flourished in Spain 500-600 years ago developed the concept that Hochma, Wisdom, Knowledge and Progress, have to go hand in hand and be combined with Hesed, Mercy, in the sense of helping people. If this fantastic knowledge and wisdom that is currently evolving is not used to cure diseases and eliminate suffering, it will be an imbalanced knowledge and will not fulfill its merciful aspect. However, I may add that in this process of "playing God", we should not lose perspective and should be humble and sensitive to human life and human dignity. We should work toward improving creation rather than damaging creation.

I would like to finish with a little tale from the Midrash: When God created Man, he showed him all the trees in the Garden of Eden and said to him, "See how beautiful and excellent they are. Be careful not to damage or destroy my world, because if you damage this world, there will be nobody else to fix it after you".

PROTESTANTISM AND THE HUMAN GENOME PROJECT

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ABSTRACT

"Genetic Science in the benefit of Mankind" and "Biotechnology: its challenges to the Churches and the World" are two documents published respectively by the National Council of the Churches of Christ of the United States and by the World Council of Ecclesiastical Sub-unities. Both reports consider ethical and legal aspects derived from projects on human genetics, such as the one concerning the human genome. The latter of these considers matters such as the prohibition of choice of sex or warnings on possible social discrimination which knowledge of the human genome may give rise to, amongst others. Protestantism holds that human life is sacred. At a given moment, this Protestant dogma could restrict scientific research. However, the Human Genome Project, as a source of knowledge, does not in principle violate the sacred aspect of life; on the contrary, it may contribute to health.

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Protestantism is very much like a speech I once gave. Someone graciously characterized that speech a thirteen points in search of an outline. Except Protestantism is worse. It defies restricted by any outline. It is by its nature an exploding star, not a polar magnet. Or, to change the image, it is always birthing new social and religious movements.

It is this multiplicity that makes defining Protestantism and Protestantism's perspective on any issue a little like trying to nail a pudding to the wall.

Yet braver and wiser persons than I have tried. They have sought for central, underlying principles. They have searched for unifying points. One such thinker was the late Paul Tillich, a theologian born in Germany who immigrated to the U.S.A. in the 1930's. Tillich characterized Protestantism in this way: *"What makes Protestantism Protestant is the fact that is transcends its own religious and confessional character, that it cannot be identified wholly with any of its particular historical forms."* (That makes an asset out of a lia bility) He continues, *"The Protestant principle, in name derived from the protest of the 'protestant' [of the 16th century] against decisions of the Catholic majority, contains the divine and human protest against any absolute claim made for a relative reality, even if this claim is made by a Prostestant church."* (Tillich, pp. 162, 163).

Tillich's descriptive and normative perspective is this: *the* Protestant principle is the refusal of and the rejection of any attempt to, absolutize the relative. That negative assertion rests, of course, upon a positive claim of faith, that is, that humans are rightly related to God when they acknowledge themselves grasped by a Power which is unconditional and which manifests itself as the ground and judge of their existence and of all that is. So stated, this double-sided Protestant principle has both critical and constructive elements.

Tillich's Protestant Principle is, of course, in reality a universal and formal principle, not limited to Protestant churches. Indeed, it has often been forgotten and cast aside by Protestants. But it remains as a principle to be brought to bear on all of life. The warning against absolutizing the relative –whether it be a theology or philosophy, an institution, a political state, a mode of inquiry, an ideology, or a particular person– is a sentinel against absolutism and totalitarianism. It is a deflator of all human pretensions. The principle begins at the threshold of one's selfhood and that self's pretensions. But it roams widely over all arenas of life. In theological terms it is a rejection of idols –penultimate powers, forces, people and theories that claim, or to which we attribute, ultimacy. *"You shall have no other gods before me."* The Protestant principle can be loosed from its moorings in the Protestant communities, but it is to be nourished and promulgated there. But whenever it appears it is the religious dimension of human life.

Faith claims of Protestantism give material content to this religious dimension. The positive claim is stated in a variety of ways. But a persistent Protestant way of speaking is to affirm that the Ultimate Power is good, seeking the fruition of the whole creation and disclosing in Jesus of Nazareth and his dealings, out of his tradition, with his contemporaries, the way to and the goal of that fruition. Further this God -spirit- is still at work, calling and enabling the community of creation to realize that fruition. Such ongoing activity requires that humans take new information and historical developments be taken into account and be evaluated in the light of normative theological and ethical traditions. It requires a community under the discipline of *reformata, semper reformanda*, "reformed, always being reformed."

Given the Protestant principle, it would be more than presumptuous, it would be ludicrous, for any one person to claim to represent Protestantism. It would be a contradiction in terms, since the dynamic in the Protestant religious movement has led to the burgeoning of religious groups, each one flying the flag of Protestant, but not necessarily saluting other standards with the same marking. So for a presentation like this the first decision to be made is to determine that source or sources one invokes when inquiring about Protestantism and the Human Genome Project.

Fortunately, one source readily at hand is documents of conciliar bodies. Two in particular are pertinent. The first is a Policy Statement of the National Council of Churches of Christ in the U.S.A. entitled "Genetic Science for Human Benefit". The second is a report by the World Council of Churches Subunit on Church and Society, entitled "Biotechnology: Its Challenges to the Churches and the World". The date of the former is 1986, the latter 1989. Both documents review issues arising from this and other projects, identifying ethical issues and bringing ethical judgments to bear on those issues. As the latter document is more comprehensive and recent, I will use it as a basic source. It should be underscored that the identification of issues and the ethical responses proposed have no coercive standing for Protestants. Their effectiveness, if any, lies in their persuasiveness. There are no institutional religious enforcement procedures, no external disciplines built into a Protestant perspective, no matter who develops or propounds it. "*God alone is Lord of the conscience*" remains a bottom line affirmation for Protestants.

In turning to the World Council paper, I will summarize the paper's recommendations and offer brief comments about ethical concerns and principles that inform these judgments:

The World Council of Churches, recognizing the potential dangers as well as the potential benefits of many forms of biotechnology, encourages its member churches to take appropriate action in their own countries to draw these matters to public attention, and to help governments, scientists, universities, hospitals and corporations to develop suitable safeguards and controls.

In particular it:

a) Calls for the prohibition of genetic testing for sex selection, and warns against the potential use of genetic testing for other forms of involuntary social engineering.

b) Draws attention to ways in which knowledge of an individuals's genetic make-up can be, and in some cases, is being abused by becoming the basis for unfair discrimination, for example, in work, health care, insurance and education.

c) Stresses the need for pastoral counselling for individuals faced with difficult reproductive choices as well as personal and family decisions resulting from genetic information concerning themselves or others.

d) Proposes a ban on experiments involving genetic engineering of the human germline at the present time, and encourages the ethical reflection necessary for developing future guidelines in this area; and urges strict control on experiments involving genetically engineered somatic cells, drawing attention to the potential misuse of both techniques as a means of discrimination against those held to be "defective".

e) Calls for the banning of commercialized child bearing (i.e. partial and full surrogacy) as well as the commercial sale of ova, embryos of foetal parts and sperm.

f) Advises governments to prohibit embryo research, with any experiments, if agreed, only under well defined conditions.

g) Encourages its member churches and other groups to keep themselves informed on how new development is reproductive technology affect families, and especially women, and develop a pastoral ministry to counsel people facing these issues, including those who choose, or are pressurized into, utilizing such reproductive techniques.

h) Believes that animal life-forms should not be patented and calls for further study of the profound moral and social implications of patenting life forms.

i) Urges the swift adoption of strict international controls on the release of genetically engineered organisms into the environment.

j) Calls on nations throughout the world to cease all use of genetic engineering as part of any biological or chemical warfare research programme, and to reconvene conventions on biological and chemical weapons in order to create new and effective protocols which prohibit their development, production and use.

k) Resolves to initiate consultations between international organisations, non-governmental organisations and scientists, with the churches and other, to reflect on the political evolution of biotechnology and its impact on global justice, and to make proposals for maximizing the benefit to those who are most in need.

(Approved by WCC Central Committee, July 1989)

These recommendations and proposals refer to matters that include but are not restricted to the Human Genome Project. That such is the case reflects the perspective that the Human Genome Project should be dealt with as a subcategory of the new biology and its technology. But it is to the specific references to the Human Genome Project that I turn now.

A major concern of the WCC paper arises from Francis Bacon's observation that knowledge is power. Certainly that is the case in a project than charts the Human Genome. To know the human genetic map and how to manipulate it is power indeed. Such knowledge may also be interesting, aesthetically pleasing, delightful and satisfying of curiosity. But it is always power. And power is to be used. The questions about power are recurring. Three are: " What purpose will this power serve?", "Who will benefit?" and "What limits are there to is?". The purpose to be served and the distribution of benefits are critical ethical questions for Protestants as for others. These enduring issues of goal(s) to be sought and of distributive justice (the proper allocation of benefits) are central for the WCC paper.

An issue previous to specific goal and to justice is that of the legitimacy of the Human Genome Project itself. Because the focus of the WCC paper is on the ethical issues arising from the application of information already or prospectively attained, it does not address this question. But the paper from the National Council of the United Churches of Christ in the U.S.A. does give it a glancing blow.

Under the heading of "Limits to Knowledge, Limitation on Research and Production", the policy statement comes down firmly

on the appropriateness of limiting inquiry and research. The document reads as follows:

Limits to knowledge, limitation on research and production

"We cannot agree with those who assert that scientific inquiry and research should acknowledge no limits. All that can be known need not be known if in advance it clearly appears that the process of gaining such knowledge violates the sanctity of human life. Remembering its own history, the church should not oppose scientific advance, but it must speak out in judgment when the quest for new knowledge supersedes all ethical concerns. We do not allow this stance to be called, not to become, one of anti-intellectual or antiscientific bias. Neither do we imply that genetic scientists are morally irresponsible, or that institutional review boards cannot make proper decision on research protocols."

In this paragraph the first principle involved is the affirmation of the positive value of scientific inquiry and research. It is asserted, not argued. The second is the sanctity of human life. The latter is the limiting principle for the former. For this Protestant policy, the sanctity of human life provides justification for determining when scientific inquiry and research must cease and desist. That limitation cashes out in subordinate propositions that would, for example, reject inquiry wich requires the use of humans as unwilling guinea pigs for experimentation. In brief, the controlling ethic of this limiting position is one called deontological. That refers to the elevation of certain obligations or rules as requiring consent and obedience in and of themselves. There is no reference to justification by a goal, that is, of a teleological preference, which measures the validity of actions to be taken solely by their contribution to the end to be obtained, whether that end be knowledge for its own sake or knowledge in order to advance the greatest good for the greatest number. The sanctity of human life is, therefore, a principle that rejects calculations of merit/demerit in terms of acts to be done in the light of goals to be realized. No end can justify in advance any means. The sanctity of human life stands as the limiting principle of scientific inquiry. It leads to an ethic of restraint and caution with reference to approving inquiry.

Given, however, that the mapping of the Human Genome does not violate the sanctity of the self, e.g., its autonomy, there is no reason in principle to refrain form undertaking, participating in, and completing the venture.

What neither of the Protestant statements tackle is the issue of the legitimacy of the project in terms of its worth compared to

other projects. That determination is a justice issue, one of estimating its value in terms of potential consequences of one inquiry over against another, and the consequent establishing of priorities for research.

To return to the question of goals to be sought and of justice to be done, two prominent Protestant ethical directives can be seen at work in the WCC paper. The first treats goals, the second justice.

Under goals there is more a warning than a directive. It is that the projection of goals to be served by information about the Human Genome is inevitably subjet to bias. *"The history of genetic movements, from Plato to the present day, shows many examples of individuals and groups, including scientific leaders and often so-called experts, who institutionalized their prejudice of race, sex, and class through programs that caused tragic harm"* (WCC, p. 14) Such a recognition elevates caution and restraint over against any particular positing of goals. Knowledge is power. That is one familiar saying. But another is also pertinent. *"Power tends to corrupt and absolute power tends to corrupt absolutely"*. There is a healthy skepticism to come into play when any one person or group proposes a goal to be sought through the application of a body of knowledge. The temptation to absolutize the relative is testified to by the history of eugenic policies.

On a more positive note the Protestant concern for justice as a primary value leads the authors of the WCC paper to speak a strong word on behalf of those who are relatively powerless. It does so by advocating that the therapeutic benefits of the Human Genome findings not be restricted to the wealthy nations whose powerful money leads to powerful knowledge for their use. Nor to those individuals only able to afford. The criteria for distribution of benefits proposed by the WCC include the utilization of such knowledge on the basis of need. This Protestant note of bias on behalf of those potentially left out of the benefits of research leans against the wind of benefits for the favored few –perhaps those peoples and nations that fund the project. Such a bias recalls the scientific and human community to its universalistic character. It elevates the issue of the social responsibility of scientific inquiry, the fact that use for whom and for what is inevitably part of the question of "to inquire or not to inquire". And when such enormous funding is involved from public sources, the nature of *the public* to benefit is proper and necessary.

The large justice issue for the Human Genome Project is its value por humans when compared with other scientific projects. The Human Genome Project as the recipient of extraordinary benefits (funding, status, prestige) becomes itself, quite appropriately, the center of justice debates and struggles. But that issue is not addressed by either of the papers before us.

In conclusion, the Protestant principle of refusing to absolutize the relative introduces the principle of skepticism into the projection of any goals to be realized through the harvesting of knowledge and/or its applications, and for monitoring from the beginning for consequences, methodology and benefits. As a formative movement that carries forward human values, Protestant policies affirm scientific inquiry and the contribution to health while they advocate for a fair distribution of the benefits of all such scientific inquiry and research, including that pertaining to the Human Genome Project.

A Protestant denominational policy statement adopted in 1989 contains these words, and they are perhaps an appropriate place to conclude:

> "With our new knowledge comes new responsibilities. As Jesus fed the hungry and healed the sick, we are called to follow his example and to use our new [knowledge and] abilities to bring healing and sustenance to people everywhere". (*The Church and Genetic Engineering*, p. 3)

The affirmation may be seen as a counsel of naivete and sentimentality by the cynical. But it may be grasped as a councel of profound importance by those whose search for human well being is both the shining star guiding their research and also the subterranean motive of their often unexamined, unnamed but powerful faith.

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THE CONCEPT OF THE "I"

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BIOLOGICAL DETERMINISM AND THE CONCEPT OF SOCIAL RESPONSIBILITY. THE LESSON OF CARRIE BUCK

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ABSTRACT

Carrie Buck, a young girl who was diagnosed as being mentally deficient, was sterilized to avoid transmission of this deficiency to her descendants. Her case passed into the history of law. The idea of achieving improvements and eradicating problems enveloped the case, both these ideas being of a social type. Nevertheless, this and other experiences have shown how erroneous it is to attempt to reduce human life to biology, disregarding ethical and social considerations on which human rights are based. In this sense, the Human Genome Project must display respect for life and overcome the diverse inaccuracies of the eugenesic movement.

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Carrie Buck, a young girl who was diagnosed as being mentally deficient, was sterilized to avoid transmission of this deficiency to her descendants. Her case passed into the history of law. The idea of achieving improvements and eradicating problems enveloped the case, both these ideas being of a social type. Nevertheless, this and other experiences have shown how erroneous it is to attempt to reduce human life to biology, disregarding ethical and social considerations on which human rights are based. In this sense, the Human Genome Project must display respect for life and overcome the diverse insidencies of the eugenesic movement.

In 1927 a young woman named Carrie Buck was involuntarily sterilized. She was the first person to be subjected to that surgery under the authority of a Virginia law. The law allowed the state to impose sterilization on persons diagnosed as being incompetent and found to be likely to genetically transmit physical, psychological or social deficiencies to their offspring. Carrie Buck had ben committed to an institution for people diagnosed as "feebleminded". The commitment followed her giving birth to an illegitimate child. Carrie's mother had been committed to the same institution some years earlier. Her institutionalization apparently resulted from prostitution and other socially unacceptable behavior. It was reported that Carrie's infant daughter also showed signs of being mentally deficient.

To the physicians, lawyers and politicians who wished to see the Virginia sterilization law constitutionally validated, Carrie Buck seemed to be the perfect person for the test of the law. The argument could be made that her mother was mentally deficient, that Carrie was mentally retarded and that her baby showed signs of feeblemindedness. This evidence of genetic transmission of their inferiority would then be presented as illustrating the need for an involuntary sterilization statute. The judgement of those who selected Carrie for the test case proved to be sound. The Supreme Court upheld the constitutionality of the law in the case which came to be known as *Buck v. Bell*. In delivering the majority opinion in the decision, Justice Oliver Wendell Holmes wrote:

> "We have seen more than once that the public welfare my call upon the best citizens for their lives. It would be strange if it could not call upon those who already sap the strength of the State for these lesser sacrifices, often felt to be much by those concerned, in order to prevent our being swamped with incompetence. It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes..."

The sterilization of Carrie Buck achieved a place in legal history and in the annals of the social sciences. The saga of social Darwinism and eugenics in the United States, indeed in the world, simply cannot be told without reference to the Supreme Court decision in her case. The fact that the legal integrity of compulsory sterilization was endorsed by the highest court in a country that prided itself on its commitment to individual freedom had a global impact. Carrie, as the subject of the case, became an historical figure of international fame. Carrie, the person, lived a life marked by what had been erroneously claimed of her and what was decided about her by people of power and influence. These

people, however, had little understanding of her true character and abilities. I will try to illustrate this later in my remarks.

Carrie was followed by thousands of other people who were sterilized under the provisions of the law. Virginia's law also became the model for sterilization statutes in other states. A conservative estimate is that 50,000 people were sterilized in the United States by the authority of these statutes. Ultimately the Virginia law was the model used as part of the Nazi Race Hygiene Program. On July 14, 1933, the model sterilization act developed by eugenics advocate Harry Laughlin, the same model used by Virginia, became law in Germany.

The Nazi law was implemented swiftly and broadly. By the end of the first year that it was in effect, according to S.J. Holmes, over 56,000 people had been found to be defective by special hereditary health courts and had been sterilized. Hitler's race hygiene programs were applauded by American eugenicists. Sterilization proponent Paul Popenoe felt that the Nazis were following a policy that was consistent with the best thinking of eugenicists throughout the world. K.M. Ludmerer quotes an editorial statement from the American publication, *Eugenical News*, that concluded, "It is difficult to see how the new German Sterilization Law could, as some have suggested, be deflected from its purely eugenical purpose, and made an 'instrument of tyranny' for the sterilization of non-Nordic races". It would be many years before most American eugenicists would comprehend the connection between their own work and the stark atrocities of the Nazi regime. It is estimated that between 1933 and 1945, two million people were declared defective and were sterilized by the Nazis. Perhaps it is because of the awfulness of the other atrocities committed during this period that so little attention has been focused on this reality. The dimensions of this infringement on the basic rights of so many human beings are, however, staggering. Recognizing that the legal, social and scientific sources of this practice were largely American is, for this American, chilling.

Otto Hofmann, a high ranking SS officer, was one of the facilitators of policies aimed at what the Nazis conceptualized as the "final solution to the Jewish question". He has head of the Race and Settlement Main Office of the Reichsfuehrer-SS. The fifth volume of *Trials of the War Criminals Before the Nuremberg Military Tribunals* contains records of the conviction for war crimes of Otto Holfmann. It states that the evidence "establishes beyond any reasonable doubt Holfann's guilt and criminal responsibility for the following criminal activities pursued in the furtherance of the Germanization program: "... forcible abortions on Eastern workers; taking away infants of Eastern workers; the illegal an unjust punishment of foreign nationals for sexual intercourse with Germans; [and] hampering the reproduction of foreign populations [forced sterilizations]...".

While the fifth volume of records of the Nuremberg Tribunals contains the conviction of Otto Hofmann, the fourth volume includes documents which were entered in his defense. Among them is an abstract prepared in 1937 by the Information Service of the Racial-Political Office of the Reich Administration. It concerns what are called "Race Protection Laws of Other Countries" and appears to have been entered as evidence on Hofmann's behalf to show that the practices he engaged in during the war were based on precedents from other "civilized" nations. It contains a litany of sterilization policies from countries including Deamark, Finland, Norway and Sweden. The litany ends with a detailed discussion of sterilization laws in the United States. It references the decision in Carrie Buck's case.

"UNITED STATES OF AMERICA

> ... Those affected by the law were primarily criminals, feebleminded, insane, epileptics, alcoholic and narcotic addicts, as well as prostitutes. Although almost all states try to carry out sterilization on a voluntary basis the courts have more than once ordered compulsory sterilizations. In a judgement of the Supreme Court of [1927]... it says, among other things: 'It is better for everybody if society, instead of waiting until it has to execute degenerate offspring or leave them to starve because of feeble-mindedness, can prevent obviously inferior individuals from propagating their own kind. The principle justifying compulsory vaccination is broad enough to cover the severing of the Fallopian tubes".

The words of Justice Oliver Wendell Holmes in this context are a sobering remainder of the credibility bestowed upon eugenic philosophy and policy, and the atrocities committed, as Daniel Kevles has so well described it, "in the name of eugenics".

Holmes in writing the majority opinion in *Buck v. Bell* used the now famous phrase, "three generations of imbeciles are enough". His reasoning and language were consistent with the eugenic view that many socially undesirable traits, including mental retardation, were largely hereditary. Inherent in this view was the idea that even complex human traits could be traced to simple genetic causes. Eugenicists believed, in fact, that most humam characteristics could be linked directly to single genes. They held that not only physical traits like eye color and height, but also personality attributes were determined by a single gene. This confidence in Mendelian genetics was extended to the determination of occupational preferences, academic interests, talents, and even character strengths and weaknesses. It was claimed that mechanical skill, artistic and musical ability were simple recessive gene traits. "Shiftlessness" was also included in this list of recessive traits. Violent temperament, it was reasoned, must be a dominant gene trait since it does not skip generations. In a study entitled *The Nam family: a study in Cacogenics* Charles Davenport re-

ported that laziness was a dominant trait, while abusive drinking and shyness were simple recessives. These enthusiastic excursions into biological determinism and reductionism may sound humorous when viewed from our current perspective but they were the basis for great human tragedy. Such simplistic views about human beings were inherent in the conviction that sterilization would help stem a feared flood of incompetence resulting from genetic blight, and they were used to stereotype whole classes of people.

While the eugenics movement was obsessed with race and ethnicity, it also focused on perceived differences in social classes within racial and ethnic groups. In her book, *White Trash: The Eugenic Family Studies*, Nicole Hahn Rafter portrays the family degeneracy studies which were conducted as part of the eugenics movement in the United States as having been focused primarily on lower class caucasian families, on the "poor white trash" of early twentieth century America. When Carrie Buck's case was first heard a report was submitted as testiomony by Harry Laughlin, the author of the model sterilization law that Virginia has adopted. He had analyzed information on Carrie and her family and he offered his report in support of her being sterilized. In commenting on her heritage, Laughlin, said, "These people belong to the shiftless, ignorant and worthless class of anti-social whites of the South... [they are an] ignorant and moving class of people...".

Henry Goddard in his book on the Kallikak family made the following comments about the kind of lower socio-economic class people who were the subjects of his study: "If all of the slum districts of our cities were removed tomorrow and model tenements built in their places, we would still have slums in a week's time because we have these mentally defective people who can never be taught to live otherwise than as they have been living. Not until we take care of this class and see to it that their lives are guided by intelligent people, shall we remove these sores from our social life".

It was on the basis of these beliefs and this reasoning that Carrie Buck was sterilized. Thus the precedent was established for the suspension of the rights of some individuals and classes for the protection of society. These views, with the credibility afforded them by being grounded in what was accepted as scientific fact, became powerful forces in shaping public opinion and social policy.

The eugenic evidence and predictions in Carrie Buck's case have proven in my own investigations, and those of others, to be grossly inaccurate. Carrie's child, Vivian, alleged to represent the "third generation of imbeciles", actually grew to be an attractive child who was a honor roll student. Carrie, charged with being the second generation of imbeciles, was paroled after her sterili-

zation to a mountain village where she soon married the deputy sheriff. There she lived a modest, but productive and respectable, life. Following the death of her husband she movel to a larger town where she earned her living caring for elderly and chronically ill people. Friends and employers attested to the fact that Carrie Buck was not mentally deficient. Indeed, mental health professionals who observed her late in her life found no evidence of mental retardation. A bit more research, in fact, on the part of those who claimed to have found defectiveness to be innate in Carrie's genealogy would have uncovered a quite different picture. If the eugenic field researchers in her case had looked just two more branchings back on Carrie's family tree they would have discovered that her grandfather and great grandfather in the Buck line were both prosperous farmers. Analysis of another branching back would have revealed that, ironically, she was descendent from one of the most prominent families in Virginia's history.

Carrie's story is a tragic saga of one injured life. It is also an important illustration of the allure and dangers of biological deterministic thought. The lawyers, physicians and scientists involved with the case were not sinister figures intent upon doing harm to this woman or the class of people she represented. They were convinced that they were serving the best interests of society by their actions. They saw in Carrie's life what they expected to see, and they used it to advance a scientific and political position that they felt would lead to the eradication of social problems and prevention of suffering. They were wrong. The idea that created the misfortune of Carrie Buck has repeatedly produced tragic results. That idea is that human life can be guided by the realities of biological determinism. The result has been that some families, some nationalities, some races, some ethnic groups and some social classes have been viewed as being naturally, inherently, and unmodifiably inferior. It has been on this basis that they have been deprived of their dignity and rights.

Robert Cynkar has noted that Justice Oliver Wendell Holmes in 1920, seven years before the decision in *Buck v. Bell*, observed, "The law is the witness and external deposit of our moral life. Its history is the history of the moral development of the race". Cynkar also quotes Holmes's book published in 1881 entitled *The Common Law*. On the first page of that book Holmes said:

> "... The life of the law has not been logic; it has been experience. The felt necessities of the time, the prevalent moral and political theories, intuitions of public policy, avowed or unconscious, even the prejudices which judges share with their fellow-men, have had a good deal more to do than the syllogism in determining the rules by which men should be governed... it cannot be dealt with as if it contained only the axioms and corollaries of a book of mathematics".

The Human Genome Project will most certainly result in scientific knowledge and medical capabilities which will bring into question the issue of "felt necessities" in relation to fundamental values. The technology of tubal ligation and vasectomy were developed in the 1890s, by 1927 it was a "felt necessity" of society that those deemed defective on the basis of eugenic science must be sterilized. The Human Genome Project will provide insights into human nature with a validity incomparble to the inaccuracies of the eugenics movement. It will provide for the development of technologies which will eclipse anything that medicine has known before. The potentials for human benefit are obviously enormous. I t seems to this observer, however, that the greatest challenge posed by the Human Genome Project will be to conduct its work and provide the benefits of its efforts to a world of people who are seen as much more than the sum total of their biological components. To rise above the temptations and dangers of biological determinism we must continue to see people, with all due respect to B.F. Skinner, as agents of freedom and dignity.

Our first commitment must be, I believe, to basic human rights and values. Even when the capacity to intervene expediently in the lives of others seems to be best for them and society; even when the "felt necessities of our times" seem to urge us so compellingly to act quickly and efficiently, this must be true. The ethical foundations of human life are to be found in human sources. The eugenicists looked to evolutionary theory and Mendelian genetics for moral truths. They felt that natural selection and Mendelian gene distributions could provide models for social ethics. The failure of this approach was evidenced in the needless institutionalization of those deemed to be "unfit" for the social "struggle", in the sterilization of people inaccurately assessed to be the carriers of defective genes and in the moral horrors of the holocaust.

Moral and ethical agency is an attribute of people, not of science or the scientific method. The recognition that we are ethical and moral agents, and that the decisions of what we sould do, as opposed to what we can do, rests with us as people in intimidating. On the other hand, it is exciting. I believe this meeting is an expression of that recognition. As the power of science for human benefit grows through the work of the Human Genome Project, so grows the importance of ethical questions about the use and yield or that power. The great significance of this conference may be the opportunities it provides for exchanges between people who are motivated by the making of discoveries, and those who seek to understand the human truth of those discoveries. I am honored to be a participant in this forum, and I feel a sense of exhilaration at the potential that these conversations will have for the future. I am

also grateful for the importance that the opportunity to speak with this distinguished gathering bestows on the life of a poor, uneducated woman who devoted her life to caring for others, my presentation to you is dedicated to Carrie Buck.

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THE HUMAN: A PROTESTANT CHRISTIAN VIEW

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ABSTRACT

The deciphering of human genetic composition probably poses once more the question of what man really is. This is an old question on the human that can clearly be interpreted from a religious viewpoint. This analysis begins with the premise that man was created in the image and likeness of God, from which solutions derive that can be understood from the political-social and biological points of view. However, Protestantism also grants man an active role as the administrator of creation. This function can be understood as a capacity to manipulate and it is this interpretation that should be carefully analysed if it is not to become a moral justification for certain applications of science and technology. On the contrary, it is a capacity that should be impregnated with humility, also bearing in mind that man, the scientist, confronts problems with the category of mysteries that are hard to solve. Religion and science, therefore, have a common aim: man.

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This paper will begin with Miguel Cervantes and conclude with a reference to W.H. Auden, distinguished authors, representatives of distinctive historical eras. In between a perspective based on a Protestant construal of the world will be offered. The intended result is an exploration of how one religious tradition, and that far richer and varied than can be suggested, may, can and should respond to the Human Genome Project with reference to the question of the human.

Religion as I am using the term means the human attempt to affirm and to deal with, through ritual, intellectual actions, and moral behavior, an Ultimate Power whose intention is good. By Ultimate Power I mean a force that is able to accomplish its own purposes and is finally not subject to the control or manipulation of other powers. The appropriate terminology for such an Ultimate Power is God.

Theology, talk about the Ultimate Power, is understood here as a way of construing the world so that the critical reference point is what is confessed to be god. A Protestant construal of the world means that the critical reference point is the God who is known uniquely in Jesus Christ as mediated through a particular tradition. That tradition gives uncommon place of importance to the reflection and behavior of those reforming movements in Western Europe of the sixteenth century, C.E., movements with leaders such as Martin Luther and John Calvin. To locate oneself in that tradition is not to claim superiority for it. Nor is it to restrict one's resources to it. It is to recognize that our reflection about God and humans is inevitably and self-consciously historical.

Miguel Cervantes, 1547 to 1616, lived in the midst of an historical earthquake, one where the tectonic plates of human definition were shifting. Milan Kundera, a contemporary Czech born novelist has written:

> "As God slowly departed from the seat where he had directed the universe and its order of values, distinguished good from evil, endowed each thing with meaning, Don Quixote set forth from his house to a world he could no longer recognize. In the absence of the Supreme Judge, the world suddenly appeared in its fearsome ambiguity; the single divine truth decomposed into myriad relative truths parceled out by man. Thus was born the world of the Modern Era".

James Wall, editor of *The Christian Century*, a weekly religious periodical, commenting on the above question, suggests that the publication of *Don Quixote* anticipated the agony of a civilization that traded certainly about God for the tainted ecstasy of human control. (Wall, p. 531).

If there were windmills rather than knights to be challenged by the man from La Mancha, the reality was not in the external

but in the internal landscape. It was the way one saw that made all the difference. And the Modern Era had a way of seeing the world, including the human, that differed from its historical predecessors. It had as well, since seeing and valuing are related, a different hierarchy of values. Now the freedom and autonomy of the individual self as a decision maker was affirmed rather than his or her subordination to external centers of authority. Liberation from oppressive institutions was proclaimed and consolidated. Human reason broke the constrictive bonds of custom and religious pretensions to be the mediator of truth in the diverse realms of life. And the new human, exulting in a new self-understanding, became the explorer and colonizer of worlds vast and minute, at once fearsome and beautful. The new self became simultaneously a humble servant, indeed a mendicant, before knowledge, and a Promethean hero who would do all things. Modern science and technology were this self's extensions and expressions. And if modern science and technology were as attached to the purposes and powers of commerce and national interests as to disinterested endeavors, the pay off was clearly for all. Or so it was assumed, though the spoils of the new era were unevenly distributed and the struggle of the scientists was not without its setbacks. But in the modern era, with all its dreadful ambiguity, humans were in control.

Don Quixote was confused. His story was question mark about the contours and consequences of the modern world. Later colonizers of the new era would see clearly what Don Quixote vaguely sensed. The icons of the new era were neither cathedrals nor thrones. They were laboratoires and factories, symbols of the rule of science and technology.

In the modern era science and technology (applied science) were regarded not only as ways of knowing and doing. They became a dominant and in some cases an exclusive paradigm for knowing and for being in the world. To be human was to know by means of observation and measurement, under conditions of causality, and then to apply what had been observed and measured to specific goals. Its yield has been incredible advances in the way we live –modern medicine is but one, but surely one profoundly important, example of its achievement.

The consequences of this way of being human were not without their costs. To the surprise of many, irrational forces were unyielding before reason's advances. Indeed such forces found slight resistance in recruiting the most advanced of what was known, and its most skillful application, to the engines of destruction and to narrow commercial interests. The dark underside of the human lay beyond the grasp of this modern way of being human. Indeed it is the very consequences of modern science and technology that have provoked the human question rather than answering it. Negative examples of that provocation were the

Nazi movement's use eugenics, and Hiroshima, though I do not equate these in any other way than this: both raised dramatically the question of what it means to be human.

The project we address this week has a similar function. It is the question of the human that is stimulated, not answered, by the knowledge of our genetic structure. Surely the philosopher's mandate, "Know thyself", meant more than the injuction to know our biological composition, its structure, process, and content. It meant more than to measure the genetic stuff which shapes us. It meant rather to take full measure of ourselves, of who we are as human beings. The ancient question stimulates modernity to become post-modern. Such an era incorporates observation, measurements, and application into a more comprehensive view of the human. It refuses the reductionism of exclusivistic epistemologies. It encourages us to probe questions of who we are, and why and how we are to live, from a variety of angles.

To say as much is in no way to repudiate the modern era with its humanly liberating intentions and contributions. It is not to seek a time when external institutions repudiate as illegitimate the scientific, imposing by force alternate world views. It is to affirm that any dominant world view of the human finally yields both positive benefits and perennial questions. "Modern medicine", a philosopher once noted, "refreshes the problem of evil". He meant that for every cure of a dreaded disease, there is another disease waiting in the wings to dramatize not only its potency but its agentry of a destructive power than refuses to be subdued, one quaintly called the demonic. For example, to prolong life so that the normal Western life-expectancy exceeds the wildest dreams of a 19th century resident is surely a positive gain. But it is also to fill nursing home beds with those whose habitation personally is the past, some long ago era packed into chemical compositions more powerful than current stimuli, into electrical circuitry no longer receptive to new stimuli. And when that condition occurs, the definition of the human is provoked, not answered. Or, when "nothing" is possible, as it is a nuclear age, or when human mutation is in human hands, as it is increasingly, then the question of the genuinely human scurries into the picture. It begins to whisper and then to declaim, "It is one thing to say of a scientific theory. It is true. It is quite another to say, science teaches us what 'true' means" (Hartt, p. 9). In that query about what is means to be truly human, scientists join all their neighbors in a debate simultaneously transcending and undergirding the scientific and technological endeavors, questioning the view of the self as primarily one who is defined by knowing by measurement and doing by application of such measurements.

In such a search, one is grateful to projects like the Human Genome Project for raising the issue of the human so forcefully and

concretely. Who is the human whose biological being we are committed to understanding and to whose benefit, presumptively, this understanding will contribute?

In the Protestant heritage, though by no means in it exclusively, the root metaphors of the human as "Created in the Image of God" and the human as "Steward of Creation" have provided normative models. I will sketch out aspects of these models of humanity, proposing essential elements and suggestions of human beingness.

First, the human as "Image of God".

This metaphor "Image of God" draws from the Genesis account, that affirms: "So God created Adam in his own image, in the image of God he created him; male and female he created them" (Genesis 1:27). In the overall context of this verse the theological construal is of God as a generative, nurturing, and ordering power. This God is the source of human life, and accords a special place in the universe to the human species and to the individual. Both the human self and the human species embody derivative value and worth from this Creator. This givenness of value and worth is not dependent on achievement, accomplishment, or good deeds, nor is it genetically determined. It is accorded by an Ultimate Power. Thus, the self's dignity is not in itself and its accomplishments. It is bestowed. As the Protestant reformers claimed, life is justified by grace, i.e., pure givenness (Creation) and pure acceptance (forgiveness). A basic value warranted by the view of God is that of the individuality of the self and its immunity from enforced definition or determination by other humans. To be human is to receive one's own life and the whole creation in gratitude and to affirm the self's dignity. James Gustafson writes:

> "The Genesis account of the creation gives us, from a religious perspective, the most solid grounds for human dignity. Calvin, like most theologians who have attended to that account, finds it an assurance of the special dignity of our species, and a record of the divine benevolence that is directed toward us. 'We ought' he wrote, 'in the very order of things diligently to contemplate God's fatherly love toward mankind, in that he did not create Adam until he had lavished upon the universe all manner of good things'. If God had put Adam on the earth while it was still 'sterile and empty' he would not have provided sufficiently for human welfare. 'Let us make man in our image, after our likeness and let him have dominion over the fish of the sea, and over the birds of the air, and over the cattle, and over all the earth, and over every creeping thing that creeps upon the earth, says God. While theologians have disputed through the ages about which human capacity makes man in the image of God, the have not

disputed the notion that the passage warrants that high dignity which we claim for our species. Nor have they disputed that all the rest of the creation exists for our service. What higher claim for dignity can be made, from a religious perspective, than that man is made in the image and likeness of God?" (Gustafson, p. 100).

A second characteristic of the human is that the self mirrors the Creator in its freedom. The non-necessity of the creation, its giveness, leads to an affirmation that what was created and is being created arises and is sustained out of the freedom of the Creator. The Protestant emphasis on individual freedom and autonomy mirrors the freedom and autonomy of God. It is an affirmation of freedom of choice as a human capacity.

In the Genesis stories of creation the presence of the command, "Of the tree of the knowledge of good and evil you shall not eat" (2:17) presupposes freedom of choice on the part of the one being addressed. Such freedom is the given capacity of a self to exercise choice within a more or less broad/narrow band of options. But the capacity for freedom may, ironically, also lead to bondage.

For Protestants, genuine freedom has a *telos*, a purpose. According to a Protestant perspective, to be free involves responsibility. To be free is to enter into a relationship of being free *for* others. Dietrich Bonhoeffer, German theologian and martyr, wrote, "The freedom of the Creator is proved by the fact that he allows us to be free for him, and that means nothing except that he creates his image on earth". (*Creation and Fall*, p. 38) What Bonhoeffer goes on to call the paradox of "created freedom" links dependence (determinism) with freedom (indeterminism). It is against "created freedom" that humans rebel, making freedom as a capacity to choose a source of isolation and loneliness, a ground of power over against, rather than power with. But the positive value called freedom embraces the normative affirmation than the human gift of choosing is basically a declaration of a normative *telos* grounded in the possibility of directing one's self-generative capacities toward the well being of the other. One is free *for* others, as God freely is *for* others.

Third, to created in the image of God is to be created *social*. "Male and female he created them."Be created in God's image is to be created as a relational beings, a social self. We cannot be human alone. We cannot be human without other human beings. That is true biologically, psychologically, and spiritually. We become ourselves in an interactive, transactional world. We have no warrant to act unilaterally, without reference to others. We gain our humanity in dealing with other humans. Our fundamental human condition is one of plurality. Individuality arises out of social matrices.

This understandig of the as social means that a characteristic and distinctive human behavior is what Hannah Arendt called "action." (Arendt, *The Human Condition,* pp. 155 ff.) Action is the creation of a human world by conversation about the human good, engaged in by a public community. It is the legitimate "public" that has expanded down through the centuries. The public now embraces all members of a community, not just the rich, the noble, males, or a particular race. It is the public which determines its own corporate life. Thus the role of new prospect/threats for life must be submitted to the forum of public debate and decision. This public forum makes imperative the introduction, for example, of educational programs so that the public may indeed by informed and give consent to practices that affect it. All, in so far as possible, are to be subjects of policies and procedures affecting them, not objects of such. To be created in the image of God is to affirm that all people –all human creatures– are intended members of the body politic, agents of their own and other futures no matter how esoteric the knowledge.

The human as a social self is always a political self, dealing with the content of what life is to be and how life is to be shaped, treating issues both of definition and of power. It is this public which bears both the power and the responsibility to determine its own life. One consequence is that decision making about the human and what affects the human cannot ethically be left to an elite, whether scientists or ethicists, but is to be lodged with the entire body politic. The trajectory of appropriate decision makers when it comes to human germ line manipulation, for example, is the universal human community. According to this understanding, efficiency as a virtue gives way to the obligation of consensus formation.

Fourth, to be created in the image of God is to acknowledge the brokenness of that image. Humans are, in the first instance, finite, living under the conditions of limitation and death. But that is no brokenness. Brokenness is the self-induce wound in the human species. It is the persistent pretension of the self individually and colectively to assert more than it knows, claiming, for example, universal perspectives for one's own local and parochial view point. It is also the human inclination to use what falls into its hands for trivial and destructive purposes. In brief, the human is one whose condition is distorted as to purpose, will and affections. The human is one who distorts the lives of others, as well as nature. Why this emphasis here under "Image of God?". Because one knows one's brokenness when one compares one's self with the image of God, whose power, wisdom and goodness humans are called to reflect. Also, to acknowledge one's own and others' brokenness is to introduce a hermeneutic of skepticism about all moral claims, including one's own. Affirmatively, it acknowledges the human as a valuing/disvaluing

being, whose image is crucially Jesus of Nazareth, fully human, fully God.

A strong, but again not exclusive characteristic of the human that reflects the image of God, correlates with brokenness. It is forgiveness. Forgiveness is the power of restoring broken relationships, of beginning again, of being open, no evasive, about errors and wrongdoing. Forgiveness dismisses what has been hurtful, whether intender or not, and releases the forgiven and the forgiver from the web of their destructive relationships. It unites them constructively, both personally and corporately. Forgiveness does not make "things" right. It makes persons able to live in mutuality despit things they have done and will do to each other. The assumption of forgiveness is that humanness requires it for personal fulfillment and for corporate endeavors. Protestants assert that to forgive is indeed divine and therefore a human possibility and responsibility.

Finally, the image of God for Protestan Christians is one that embodies activity. Humans are to image God's activity. They do so by loving neighbors and caring for nature. They do so by struggling for justice. They do by obedient activity in all realms of life. This active perspective is in contrast to those for whom St. Thomas Aquinas articulated a different stand, namely, "[Our] ultimate felicity consists only in the contemplation of God." To be a Protestant Christian is to be, individually and with others, an active agent. It means to be a steward of God's creation.

A second root metaphor that has consequences for the Human Genome Project is that of the human as the Steward of the Creation. In Genesis the world is called good and humans are called to tend the garden of life.

The Protestant shaping of humanness and the world has been diverse. Protestantism as a term points to a cluster of reforming movements that run on parallel tracks in the 16th century and diverge increasingly thereafter. But one element of the Protestant understanding of the human pointed to by the sociologist Max Weber is the desacralizing of nature. Because God creates and trascends the creation, creation, itself has no sacred precits. This means that no arena of life, human nature or otherwise, is out of bounds, exempt in principle from investigation and manipulation. The human curiosity to know and the human desire to apply knowledge have been legitimated by a religious perspective that affirmed the human as an active agent who is called both to understand and to reshape the world. Indeed, such historians of ideas as Professor Lynn White have argued that Protestantism is to be blamed for the rape of nature, elevating the human to a status so far above the rest of nature that it overwhelmed the perspective of the human as part of nature. Limited trascendence of the human over nature was expanded to absolute transcen-

dence. The phrase describing humans as "Under God, over nature" made for considerable mischief.

Professor White's point may be well taken without Protestantism's being understood as the sole perpetrator of the misuse of nature and while recognizing that there were counter forces in the tradition as well. But the Steward of Creation as a metaphor for human responsibility for the planet earth and for wherever our power takes us remains suggestive when considering the Human Genome Project. I will briefly assert some implications arising from the metaphor.

First, the creation is not our own. It is God's. We hold it in trust for future generations and for all who are currently residents. We are to respect it and to care for it. Humans are caring creatures.

Second, to care for anything involves understanding it. For stewards, to understand becomes not just a function of curiosity but a moral claim. To understand our genetic composition is consonant with the stewardship of the creation. In principle there is no reason not to seek to understand. In fact, quite the opposite is the case. John Updike, the American novelist, wrote, *"My theory was that God knows everything and cannot be shocked. And only truth is useful."* The appropriate attitude for stewards is respect and even awe for what has been "received," and for using that we know for caring purposes. Awe and respect form the appropriate context for curiosity and investigation.

A third characteristic of stewardshis is manipulation. Manipulation means literally putting one's hand into the mix, transforming it. The steward cares for that which is the owner's. To do so means being engaged with processes, structures and products. It means altering what is, so that there may be an improvement in the product or an increase in the production or a change in the structure. It means not playing God, but being engaged *for* and *with* God. That is, of course, a presumptuos claim and one subject to abuse.

The issue of manipulation is one which refers to the use of appropriate technology to achieve stated purposes. But for the steward of creation the question is not manipulation or not, but what kind of manipulations and for what purposes. When it comes to genetic engineering, cautious underwriting of therapeutic interventions (gene therapy) by all religious communities is a reflection of the positive stance toward manipulation. On the other hand, the determination to reject human germ line interventions may be understood also as a prudent judgement, not a principled one for the steward. The issue as to where to draw the line in terms of such possible manipulation is a slippery slope indeed, but it is perhaps approached most productively on a case by case basis rather than by a general principle repudiation. For the

steward, the burden of proof of positive consequences for such a risky venture must be on the innovator who proposes change. That proof must be submitted to the judgements both of scientific elites and the public.

Further, *the ability* to intervene must not be accepted as the moral justification *for* intervening. That technological mentality is powerful in the world, taking on its own force. Bonhoeffer wrote, "Technology is the power with which the earth grips man and subdues him". In such a state humans do not rule, they are ruled, sacrificing freedom as choice and as responsibility. The technological imperative overrides other injuctions.

For example, the negative evidence of eugenic practice weights the scales heavily in favor of restraint and even refusal when it comes to human germ line manipulation. overall, therefore, what Dr. Maxine F. Singer, President of the Carnegie Institution of Washington, C.C., has called our "novel competence: the heritable alteration of cells and whole organisms... a procedure qualitatively different from what was previously possible", argues for proceeding only under the most careful controls. Because it is a *novel* competence and because it is a qualitative difference from previous practice, a stewardship of creation in this area leads to a conserving ethic and an ethic of restraint which takes itno account the sanctity of the species, not just of the individual self. Still, the issue is not, in principle, closed for public debate and decision. Such is the dizzying heights of human freedom that no such question can be closed. What is important is that such questions be "very open", not restricted to the esoteric vocabularies and decision making by the initiated few.

Finally, a steward of the creation understands that his or her position is one not of arrogance but of humility [modesty]. When it comes to biology and the Human Genome Project in particular that humility has at least two sources. One derives from the discipline itself. It is the recognition of how little we know. Lewis Thomas, physician and essayist, has written:

> *The only solid piece of scientific truth about which I feel totally confident is that we are profoundly ignorant about nature. Indeed, I regard this as the major discovery of the past one hundred years of biology. (Thomas, p.73).*

There is so much yet to know that our current knowledge is radically relativized. A second outcome of humility is the recognition of the difference between realms of knowing –even when confronted by the same data. One realm of knowing looks at our current biological knowledge and sees problems to be solved. A second looks at the living world and affirms, *"Nothing in the living world remains mysterious. We do not yet understand all we see about us, but we are reassured that it is all understandable, all describable in terms of chemistry –of molecular structure and the interaction of mole-*

cule." On the other hand, this knowledge, as was asserted earlier, raises the question, "What is the human?" Or better, "Who is the human?" An the category of mystery is introduced by scientist and other who see in the material before them what they call beautiful, awesome, and humbling.

If a protestant may quote a Jesuit, and a Jesuit poet at that, as part of protestant presentation, then it is to Gerald Manly Hopkins that I would turn. In a letter to his friend Robert Bridges who had apparently written him about something being a "mistery", Hopkins wrote: *"You do not mean by mystery what a Catholic does. You mean an interesting uncertainty. But a Catholic by mystery means and incomprehensible certainty".* (Deborah Douglas, p.10.) To that this Catholic Protestant says "Amen".

For Protestants and Catholics this incomprehensible certainty is not a passive object, to be explored and explained without remainder. It is an active force bearing down upon us in various shapes and forms, coming to us, calling to us, inquiring of us as to who we are, even as it provokes the response of a journey into an understanding, without definite comprehension, of its nature. A mystery always has surplus of meanings. We live with a mystery, like Jacob, wrestling with it, struggling with the questions mystery puts to us and living into what answers we are given. For mystery, an answer is preceded and followed by questions, forming a dynamic relationship. From the answers we give and are given flow our fundamental self-understandings. To be engaged by mystery is to be vulnerable to personal and social transformation.

Gabriel Marcel, the French philosopher, has made a useful distinction between the categories of problem and mystery. He writes:

> *A problem is something which I meet, which I find complete before me, but which I can therefore lay siege to and reduce. But a mystery is something in which I am myself involved... A genuine problem is subject to an appropriate technique by the exercise of which it is defeated: whereas a mystery, by definition, transcends every conceivable technique. It is, no doubt, always possible... to degrade a mystery so as to turn it into a problem. But this is a fundamentally vicious proceeding...* (Robert McAfee Brown, p. 262).

So understood, love is a mystery, hope is a mystery; we are mysteries to ourselves. We are not mysteries that can be "solved". We are mysteries in which we live and move and have our being. Religion and science encounter the same realities, separate in focusing attention on particular presentations of what "is", and instruct each other as they meet in the transaction of mystery and problem. Protestants claim only to call for a context of understanding more inclusive than "problem" and not as obscurantist

as an unexplored mystery, thereby opening the way to transformation of what it means for us to be human.

Perhaps the most awesome mystery that Protestants proclaim for humans is the reality that we are co-creators with the ultimate Power in a dynamic cosmos. Our calling as stewards is not to fit into an assigned slot in a passive world, but to share with others and with the power we Protestants call God in continuing the development and hopefully the maturation of the world.

A concluding word is perhaps in order before summarizing. For some of us Protestants the way to think about the human is to think from the future backward. The human toward which we live is the eschatological, the promised end, where humans live with each other an God in freedom and mutuality, where there is no weeping or crying or death, neither rejection nor loneliness, but all dwell in dynamic harmony, justice, and tranquility with their neighbors and with nature. That mystery, that promised future has reference for life and for life beyond death. Our life shudders on the presence of death. But it is the former which I shall address.

We are, according to this perspective from the end of history, currently proto-human, not yet fully human, on the way to our humanity. We are pilgrims exploring emerging worlds. We reside in the tension between what we shall be and who we are now. We make decisions in the light of what we are called to be, but also under the conditions of what has been. Thus, this future is not without content. It is the fullest expression of the life lived by Jesus of Nazareth in his dealing with his contemporaries. Its qualities are love of God and neighbor and doing justly. Its specific contours we are to unfold, but not without reference to the image of God with us in Jesus of Nazareth and made possible today and tomorrow by the same Spirit of God which animated Jesus and the community centered around and with him. Precisely in the midst of the tension between past and future we make our decisions about who we are and who we are to be, and then about what we shall do. Our habitation is, we Protestant Christians affirm, the future as powerfully as the past and the present. Therefore there is an open morphology of the human. We understand ourselves and all human as "not knowing what we shall be," but confident in the power of the one called Creator, Redeemer, and Ruler. Our decisions are laced with ambiguity. They are often harmful in their consequences, diluted in their power by our limited interests. But the Protestant affirmation of grace is that, fortunately, the way of humans lies not in themselves, but in an Ultimate Power whose will is goodness for the whole creation.

In conclusion, then a quotation from W. H. Auden. His observation reflects the modern and, I believe, the post-modern world's

grasping of the nettle of ambiguity, responsibility, and anxiety. He writes:

> *"The Distresses of choice are our chance of being blessed.* (For the Time Being)."

That we have a chance at all is grounds for gratitude, hope, and courage.

Summary: I have contended that we are residents of an emerging post-modern world, one that concedes sometimes grudgingly and sometimes gladly, the multiple ways of knowing and being in the world. The fact that this diverse group is gathered here is testimony to that new era. It is, in fact, ironic that the very successes of the so called scientific world view have elicited from within and from without the scientific community the question of the human.

In ilustrating one way of thinking about the human I have drawn from a particular historical tradition, one called Protestant Christian, without claiming exclusive rights by that tradition, and without presuming to represent the Protestant perspective, an oxymoron if ever there was one. The sum of this presentation is perhaps that the human is a complex not a simple reality, one with many characteristics. At various times various characteristics have been elevated as "the human characteristic," e.g., reason, valuing, consciousness of its own dying. Different Protestant perspectives on the human have been advanced –the self as pilgrim, the self as citizen, etc. But what seems apparent is that the human self is a cluster of characteristics all of which must be affirmed, protected and advance. Some of these were asserted with the assistance of two root metaphors.

Two root metaphors given prominence in Protestant Christianity and nuanced differently because of that setting, have been used. One is the human as created in the Image of God. The other is the human as the Steward of Creation.

Under the human as created in the image of God the following were affirmed as essential for humanness: 1) The individuality of each human being and the dignity of the self and the species; 2) freedom as a capacity to choose among options and to take responsibility for oneself and God's world; 3) the sociality of the human, resulting in shared decision for oneself and God's world; 3) the sociality of the human, resulting in shared decision making and wide distribution of power; 4) the brokenness of the self in terms of separation from its source of being, its own freedom, and its neighbors and therefore a hermeneutic of skepticism about moral claims; 5) and the human as actively engaged in the world and with neighbors.

Using Steward of the Creation as a heuristic device, I have designated these elements of humanness: 1) understanding the cre-

ation as not our own, but as having its source and being in an Ultimate Power, with our call being to care for the creation; 2) to care for requires understandig; 3) manipulation is an obligation, as is restraint, in dealing with the created cosmos; and 4) the virtue of humility has consequences that simultaneously propel both science and technology while de-imperializing them as ways of being human.

In conclusion, I affirm the proto-human nature of the human, and reassert the dynamic and pilgrimage quality of life, individually and corporately. Our confidence is finally not in ourselves, but in One whose power is proportionate to the purposes of fruition for life as we receive it, discover it, construct, and reconstruct it.

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MANKIND IN SEARCH OF MEANING

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ABSTRACT

The Human Genome Project attempts to integrate the biological point of view with that of the social sciences or, in other words, it attempts to link the subjective human world to the objective natural world. The discoveries in molecular genetics support the unicity of the individual; that is, each human being is the unique product of genes and experience. It may be asked whether scientific knowledge in the modern era will be able to shape our beliefs.

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The Human Genome Project attempts to integrate the biological point of view with that of the social sciences or, in other words, it attempts to link the subjective human world to the objective natural world. The discoveries in molecular genetics support the unicity of the individual; that is, each human being is the unique product of genes and experience. It may be asked whether scientific knowledge in the modern era will be able to shape our beliefs.

I am speaking to you not as a molecular biologist nor as a philosopher, but as a clinical neurologist. A neurologist develops a special perspective regarding the human impact of science, a perspective which I hope to share with you today. This point of view derives from our clinical work, which involves seeing patients with physical brain lesions that affect awareness and behavior in a startling variety of ways. Each day we must interpret what is known of modern brain science to patients and their families, dealing with many issues at a very practical level. From this viewpoint, at once introspective yet pragmatic, I have tried to examine how the genome projects will impact our view of the meaning of life and our place in it.

To primitive man, the whole world is alive, with wind, rain and mountain aware and purposeful. As culture develops, this animism gives way to a dualism which divides the world into the living and the non-living, the soul and the body, the sacred and the profane. In modern times we preserve this dualism as split between mind and body, or between consciousness and the physical world. This mind-body separation continues to permeate our thinking, our literature, and our philosophy, whatever else we believe or don't believe about heaven or an afterlife.

As scientific reductionism advances, dualism breaks down. Increasingly, quantum mechanics can explain chemistry in a lawful fashion, chemistry explains molecular biology, molecular biology explains cell physiology and biochemistry in a chain of knowledge linking subatomic events to the living world. In my field, I see an increasing ability of physiology and neuropharmacology to explain the various phenomena of consciousness. With the interpenetration of scientific knowledge from one link of the chain to the next, consciousness becomes an emer-



Figure 1



Figure 2

gent property of inorganic matter rather than something distinct and soul-like.

To illustrate something of where we are now, this slide summarizes data on brain electrical activity in normal subjects by Gevins' group in San Francisco. These lines represent covariance in evoked potential data from pilots squeezing a trigger with their left index finger after seeing a numerical cue. This method permits us to see the electrical activity passing from verbal processing to decision-making center, then backwards to activate brain cells involved in actually squeezing the trigger.

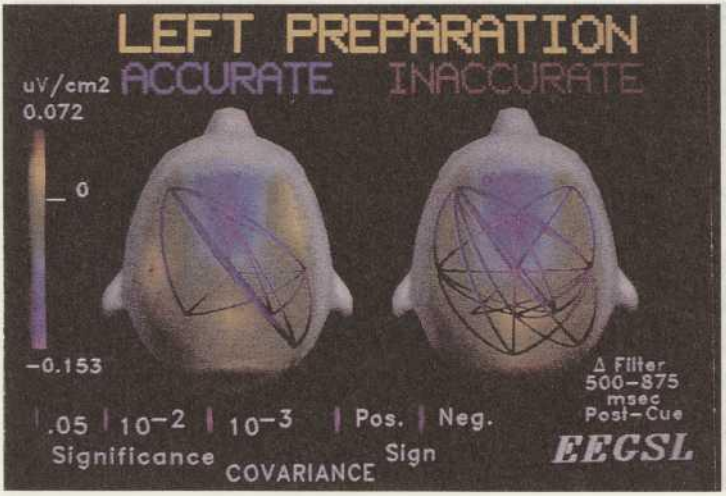


Figure 3

Of course, here we analyze a single split-second decision, not a detailed inward debate on economic theory, or even on what to have for lunch. Until we fill in more detail at many levels, the ultimate reduction of consciousness to physiology is not yet proven; so far, we still accept this reduction on faith. Nevertheless, this faith continues to be justified by the burden of evidence. Neuroscientists who study brain fuction in the laboratory, or neurologists who study "Nature's experiments" in the clinic, look at the brain as the tissue of mind, without having to postulate a "ghost in the machine" or a dual universe to explain consciousness.

Part of the enormous mythic power of the Genome Projects lies in the symbolic completion of this chain of knowledge which connects human consciousness to the inanimate universe. The ability to uncode the genome, to write a "complete recipe" for a human being, creates a powerful metaphor, powerful enough to impact modern thought at every level in society. Initially, deciphering the Human Genome seems to somehow diminish our humanity, perhaps implying that we can be controlled or transmuted, as by an alchemist's formula or spell. Certainly this genetic metaphor links us firmly and inextricably to the rest of the biosphere, implying strongly that everything about us, including our conscious experience, may be explained in biological, indeed genetic, terms.

Once we view consciousness as an emergent property of a biologic system, it becomes increasingly difficult to believe in the soul as something detachable from the body and endowed with an afterlife. How do we come to terms with our science at the level of religion, of mythology, of our daily self-image? Ultimately our world view must accomodate these concepts or else find a way to repudiate science, our single most successful activity as human beings.

Many people will indeed remain ignorant of or reject the implications of this new information, clinging to old beliefs, possibly in distorte forms. To other who accept the new information, it will present an invitation to nihilism or "existential" despair. Our challenge as a species will be to move beyond both rejection and despair, working to search for values and meaning arising from our own biologic nature rather than simply attributed to divine authority. Without the idea of an afterlife, religion loses its unfair leverage on the believer. In the future, religion or mythology will have to prove its value to us by improving our sense of meaning and self-worth here and now, without appeal to an afterlife where amends will be made for earthly wrongs.

Our modern crisis of values arises in part from our enormous success in the natural sciences. It is worth reviewing the difference between natural science and philosophy. Science studies natural phenomena objectively. Progress occurs by reductionism, that

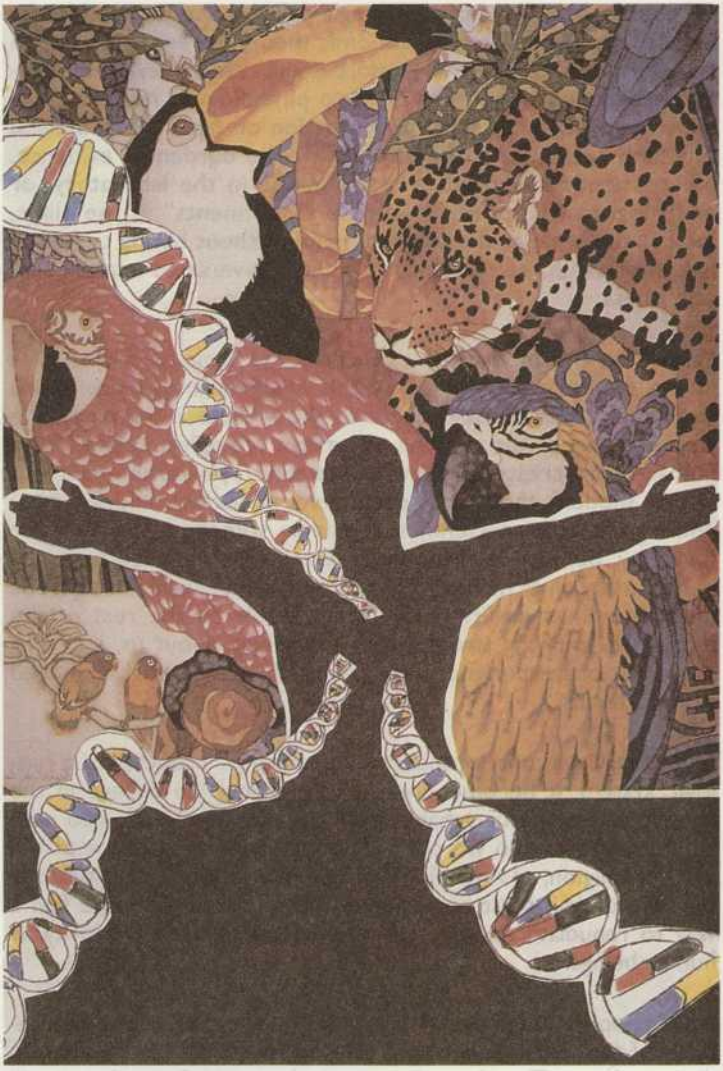


Figure 4

is by taking complex phenomena and reducing them to simpler phenomena which can then be examined quantitatively. We observe and describe the phenomena as objectively as we can, and we exclude the perspective and effects of the observer, except at the quantum level as articulated in the Heisenberg Uncertainty Principle.

Science explicitly excludes values; scientific phenomena are studied because all things are interesting, not because of specific utility or value to mankind. Part of our society's malaise may arise from the triumph of objectivity as embodied in science and tech-

nology without a corresponding success in our understanding of value and meaning.

In contrast to the objective natural sciences, philosophy studies mankind's subjective relation to the universe of natural things. Values and meanings are integral to the human world, and as one of its goals, philosophy tries to provide a rational system for determining values. From this arise meaning and meaningfulness. Mythology and religion are instinctive, visceral attempts to find meaning in our lives, while philosophy attempts to satisfy the same desires at a logical, rational level.

Philosophy and science are interdependent as human activities. Philosophy cannot create a realistic world view without recourse to the findings of natural science. One of the reasons for continuing change and ferment in philosophy is the continued need to account for scientific progress. The great philosophers Hegel and Kant made errors in the natural sciences that a first year graduate student would find laughable today, and despite the inellectual virtuosity of these and other giants we must continuously re-make our philosophy with what we learn in the laboratory.

The critical juncture between philosophy and natural science lies in the scientific study of humanity, including not only biological but also psychological, anthropological and sociological perspectives on man. In these areas, we train the reductionist paradigm on ourselves, and the realm of the subjective become the legitimate topic of objective study. Not only can values and meaningfulness be studied and to some extent quantitated, but these studies can be extended cross-culturally to examine universal characteristics of humans as individuals and in social groups.

From our perspective in this gathering today, we can presume that much or all of what is universal in mankind is implicit in the Human Genome. "Human nature" would not be human nature if it did not spring from our biologic origins and carry some measure of selection advantage, at least in the past. We must bring this perspective to bear on such intrinsically human characteristics as our penchant for violence, our romantic and family attachments, our tribalism, and our religious impulse.

A coherent "science of humanity" integrating perspectives from biology and the social sciences will tell us what is fundamental and nourishing to the spirit of mankind as well as to our bodies. This is the critical juncture where our self-knowledge from philosophy, religion and art must meet and join our self-knowledge from the natural and social sciences, so that we can create and direct our struggle to find value and meaning. In this context, the Human Genome Projects provide a critical link and a symbolic link connecting the subjective human world with the objective natural world.

TWINS REARED APART & TOGETHER: PERSONALITY VARIANCE FACTORS

SCALE	GENETIC	SHARED FAMILIAL	UNSHARED
WELL-BEING	.48	.13	.40
SOCIAL POTENCY	.54	.10	.36
ACHIEVEMENT	.39	.11	.51
SOCIAL CLOSENESS	.40	.19	.41
STRESS RXN	.53	.00	.47
ALIENATION	.45	.11	.44
AGGRESSION	.44	.00	.56
CONTROL	.44	.00	.56
AVOIDS HARM	.55	.00	.45
TRADITIONALISM	.45	.12	.43
ABSORBTION	.50	.03	.47
+ EMOTIONALITY	.40	.22	.38
(-)EMOTION	.55	.02	.43
CONSTRAINT	.58	.00	.43

Tellegen et al J Pers Soc Psych 54:1031(88)

Figure 5

I would like to present some examples of the biology of mental processes, hoping that such clues will lead us to some understanding of the genetic possibilities and limitations of human thought. Many recent developments point to the important genetic contribution to personality. This audience is already quite familiar with the important evidence for a genetic contribution in alcoholism, bipolar affective disorder, schizophrenia and other mental illness. These conditions deviate markedly enough from normal mental functioning to be called illnesses, although alcoholism lies very close to the limits of what we intuitively consider the normal range of human behavior. Mental illness has been studied earlier than genetic aspects of normal personality because of the greater ease of diagnosis and the greater medical importance of mental disorders, yet we have no reason for thinking that the intrinsic features of normal personality depend any less on genetic contributions.

A number of fascinating studies have looked at fraternal and identical twins raised together or separately. By performing studies of the personality traits of these subjects, reliable estimates can be made of the genetic and "environmental" contributions to explaining variance in personality. In one large study, for example, rather startling estamates of 40 to 55% genetic contribution were found in such components as self-image and even traditionalism. An interesting feature of this and other studies is the observation that "environmental" influence varied significantly even within the same family and household. This implies strongly that individual experience and perspective are still critically important for personality formation, but within constraints dictated by genetic inheritance.

A few examples from clinical neurology will further illustrate something about the functional organization and limitations of

the human brain. Perhaps the most obvious limitations relate to perception. Very clearly, we never directly experience reality, but only know it indirectly through our sense organs. An extensive literature exists for each sensory modality, of course, but in a general sense our perceptions are limited both in range and in modality. For example, our ears respond only to limited sound frequencies, our retinas to limited frequencies of light. Our noses are measurably less acute than in many other animals. Other peculiarities dictate many salient features of our perception. For example, the overlapping pattern of cone receptors in the retina seems to explain why the color yellow looks brighter to the human eye than other colors.

The brain actively processes its sensory input before sensation comes to consciousness. Examples have been best detailed for the visual system, where the brain not only extracts certain features of interest such as lines or specified orientation, etc., but that the brain uses feedback pathways to the periphery to control and limit sensory input. The pupillary reflex causing constriction of the pupil to bright light is only the crudest of many physicological mechanisms to reduce sensory input to a level which the brain can handle. All these mechanisms have efficient data, but without a doubt provide serious limitations on our view of reality. By examining this detail from an Impressionist painting, we see this process in action. Our visual brain uses context to turn a meaningless pattern into a visual impression of water. Imagine how different the human world view might be if we had the sonar capabilities of the bat, the high frequency hearing of the dog, or the ability to sense magnetic fields demonstrated by migratory birds!

Many examples can illustrate functional principles of human thought. The most celebrated of these principles remains the distinction in processing between left and right cerebral hemispheres (fig. 6). Simply put, the dominant (usually left) hemisphere shows a predilection for reasoning which is sequential, including logic, mathematics, spoken, written or signed grammar, etc. The non-dominant (usually right) hemisphere shows a predilection for parallel reasoning, such as that involved in reading a map, recognition of faces, non-verbal gestures, inflections, etc. Both hemispheres normally process spoken speech, for example. The left hemisphere analyzes the grammar of what is said, while the equivalent structures in the right hemisphere attend to the emotional overtones conveyed by tone of voice, facial expression, body movements, etc. If a gesture expresses emotion or emphasis, the right hemisphere analyzes this aspect; however, perform the same gesture for an individual who knows American Sign Language, and its grammatical content will be analyzed in the left hemisphere. Clinical brain injuries shed further light on the complementary function of both hemispheres; consider the example of arithmetic calculation in stroke patients. With left hemisphere lesions the numbers may

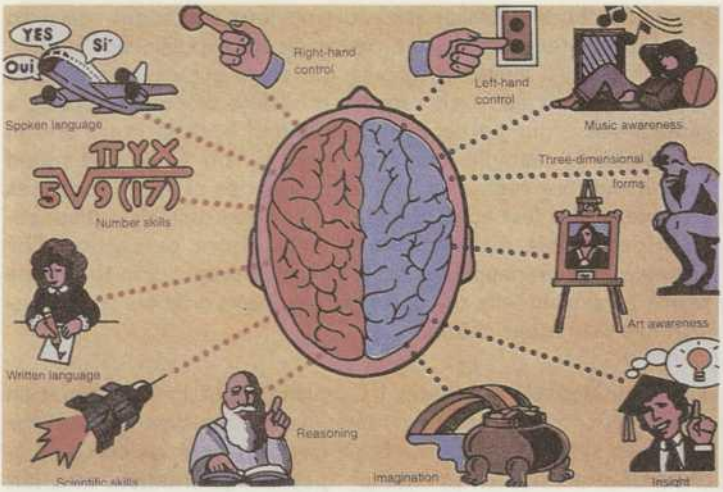


Figure 6

not be read or added correctly, but with right hemisphere lesions the columns of figures may be aligned improperly due to defective spatial relations.

Of interest, we have greater conscious access to left hemisphere functions, and much of right hemisphere processing occurs without our awareness. This leads to interesting speculations that the Freudian unconscious lies in the right hemisphere, although this idea has not been proven or refuted so far. The interplay of linear and parallel processing, as well as the greater conscious access to left hemisphere function, provide important parameters of human mental activity.

Although most of us would consider language and left-right hemispheric specialization to be critical biological features of what makes us human, gross examination of the human brain reveals only very subtle anatomic changes to account for these dramatic developments. On the other hand, be immediately struck by the rapid enlargement of the frontal (sometimes called prefrontal) lobes, comprising fully 30% of the brain in *Homo sapiens* (fig. 7).

Clearly something about the frontal lobes must have decided survival advantage, and in evolutionary time their continued enlargement predates other critical human features such as upright posture, prehensile thumb or language acquisition. The function of the frontal lobes is quite subtle, so subtle that large injuries may occur there without immediately obvious effects on our behavior, accounting for the old, erroneous belief that we "fail to use" much of our brain. Simply put, the human cortex is generally organized into a posterior "sensory half" and an anterior "motor half". Information from vision, hearing, touch and other sensory modalities comes to the primary sensory cortices in the posterior

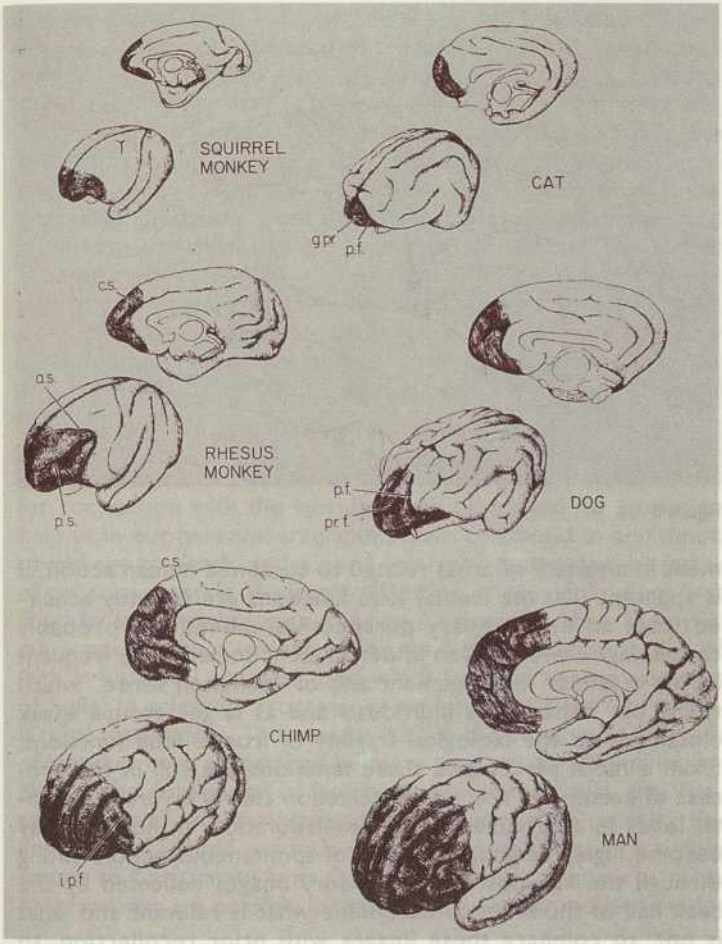


Figure 7

halves to each hemisphere (fig. 8). This information undergoes further processing and ultimately is synthesized into a coherent, integrated awareness of the exterior world and our own body's relation to it. This information is then projected forward to the prefrontal lobes where further processing initiates action, which then projects slightly backwards to reach the motor strip. The motor strip acts like a set of marionette strings to control the final motion of arms, legs and face.

What processing occurs in frontal lobes prior to action? Data from animal work and the results of clinical lesions in humans suggest strongly that the frontal lobes are the seat of decision-making, judgement, planning and projection into the future. Injuries to the frontal lobes in humans result in subtle problems which may not be obvious to physician or lay observer, but may result in a loss of ambition, a failure to gauge oneself and assumption of unrealistic goals, or important defects in judge-

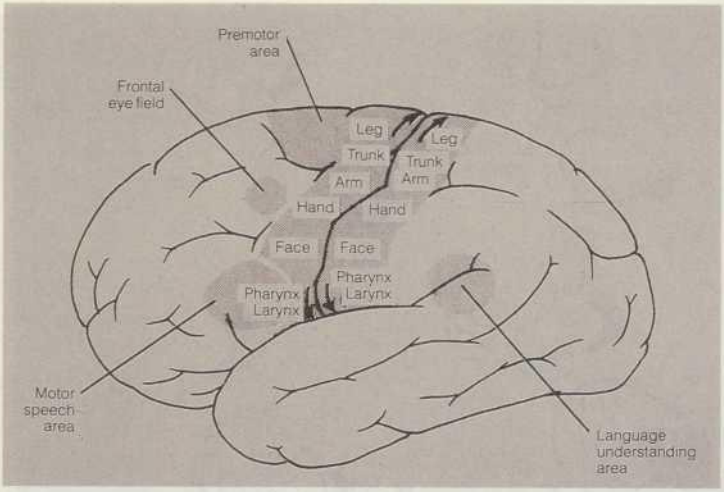


Figure 8

ment in a variety of areas related to sustained human action. It is apparent that the frontal lobe functions are recently acquired from an evolutionary perspective, indeed are probably continuing to evolve even in our present society. The frequent lapses of ethics, of judgement and of "common sense" which riddle our behavior as individuals and as larger groups speak eloquently to the biological fragility of frontal lobe functions. From a racial perspective these functions are still in the process of becoming. Yet natural selection clearly favors the frontal lobes in a sustained drive for elaboration. In humans they become highly developed agents of spontaneous action, sifting through the kaleidoscope of sensory images collected by the back half of the brain to determine what is relevant and what is not, to compare these images with prior recollection, to project various courses of action into the future, and finally to select, initiate and sustain a course of action. The frontal lobes are the engines of free choice, liberating us from a reflex response to the world around us. Further study of their subtle functions will be critical to a biological understanding of humanity.

I will move away from strictly neurologic concerns now to touch on a behavioral issue which is critical for understanding our nature, even though the anatomic and physiologic underpinning remains less clear than for what we have just discussed. This is the need to belief, for meaning in our lives. This need arises to varying degree in each of us, yet seems to cut across all societies and epochs.

To primitive man, the survival value of a predisposition towards a common belief system appears evident; shared religious beliefs have clear value in promoting family and tribal cohesion. Yet the need for a belief, for meaning, for an orientation between the in-

dividual and the world around him appears to be stubbornly persistent, even in modern society. In fact much of the malaise that afflicts industrialized society appears to result from the loss of belief, robbing our lives of meaning beyond the simple accumulation of worldly goods. An examination of mythic and religious themes from different cultures permits us to draw some conclusions about the human need for meaning. Much of our religious ideation springs from an augmentation of emotions evoked by our earliest childhood contacts with our parents. The awe of the tiny child for his father's might becomes the role of the war god or stern patriarch; the child's desire for closeness with his mother's warmth augments to become an image of a nurturing earth mother. These and other themes of birth and death, loss and redemption, run through all the stories of all the peoples of this planet.

What needs do these myths fulfill? We evidently have a need for connection with the world around us, a need for stories to help us in our personal transitions from childhood to adulthood to old age to death, and a need to access certain special states of consciousness. In Western civilization, these needs were first filled by local mythologies, then by Christianity, then later (for many people) by a variety of secular faiths, including a type of faith in historical progress itself which included varying elements of belief in scientific progress, in evolutionary progress, in dialectical materialism. This secular faith in the continuing progress of man has been threatened by many modern developments, including the domination of Europe by Hitler and Stalin, the Vietnam War and growing ecological signs that we are reaching the limits of unchecked expansion on this planet. Neither a simple return to Christianity in its current forms nor a return to naive progressivism are possible for many people in our modern world.

Some people "opt out" by losing themselves in immediate daily concerns; the "workaholic" finds meaning in work to the neglect of other values and the hedonist finds meaning in sensual experiences associated with sports, material possessions or drugs. Yet many people find something missing in their lives and this accounts for the renewed interest in Oriental religions, in the occult, in a variety of so-called New Age beliefs. How will our scientific knowledge of ourselves, symbolized by the unriddling of the Human Genome, make it possible for us to shape our beliefs and myths for tomorrow?

My own qualifications are minimal for adding to the future of this discussion; I am neither a philosopher nor an expert in religious studies. Nevertheless, to close this talk I would like to sketch in some preliminary ideas of how we may shape our values in the future.

Respect for the environment and for our connection to the biosphere must be important elements of our future mythology.

As stated, the Human Genome Project create the symbolic link between humanity and the biosphere, and a variety of ecological crises are already confronting us forcibly with our dependence on the environment. This sense of our stewardship of the Earth is not integral to Christianity as it has been practiced in the past. The Judeo-Christian denigration of nature motifs had much to do with the subjugation of the agricultural Canaanites by the nomadic Hebrews, whose religion promoted tribal cohesion as the Chosen People while subordinating oneness with Nature as an idea fit only for the surrounding agricultural peoples. Judaism and later Christianity continues the motif that Man was the link between God and a baser Nature, a Nature that must be subjugated to God's will (or at least the will of his true followers). For centuries this ethic of the conquest of Nature was a successful idea, promoting expansion, achievement and conquest, even at the expense of forests and water. Now that we are reaching the limits of expansion on this planet, a return to a more integrated view of our place in the world is not only timely, but it may become a matter of immediate survival. A return to some of the agrarian myths, to an emotional connection to the land or to the nurturing Earth Mother, will resonate with these practical needs.

On the other hand, another legacy of our Western civilization is the emphasis on the individual, which came to its first fruition with the emergence of the Renaissance from the Middle Ages. This emphasis on the value of the personal perspective proved the stimulus to unprecedented individual achievement in the arts, in science and technology, and in commerce. This fundamental change underlay the eventual overthrow of tyranny and the birth of democracy. To most of us, the emphasis on the worth of the individual is integral to our ethics and seems worth preserving, despite the element of conflict with our ideal of re-integration with the world around us. I see the advances in molecular genetics supporting the value and uniqueness of the individual, not only because of the special nature of each genetic patrimony but because of the demonstrated uniqueness of each environmental interaction even within the same family unit, as we discussed earlier in the twin studies. If each human is a unique product of gene and experience, then this reinforces our unique worth as individuals.

As religious faith and naive progressivism have collapsed. Existentialism stands as one of the most important modern answers. Jean Paul Sartre and his colleagues correctly saw the collapse of traditional values, embraced the anxiety of having to find their own meaning in a meaningless world and chose to confront this anxiety and deliberately construct their own values. While applauding the courage and incisiveness of Sartre, I feel that Existentialism as first enunciated offers much, but falls short of the answers we seek today.

First of all, Sartre emphasized the free man's unlimited freedom to choose. We have already seen that man in fact is free to make certain choices, but that these choices are constrained by biological factors, many operating unconsciously. These factors cannot be changed without altering our genetic heritage. By acknowledging certain biologic constratints on our mental and physical beings, we find ourselves much closer to the Spanish philosopher Ortega y Gasset than to the Existentialists.

From our inspection of the frontal lobes, we can see the importance of self-directed behaviours, which are only triggered indirectly and unpredictably by environmental stimuli. This means we really do have the freedom of choice that we feel we have. Within our biologic constraints, we are responsible for our choices, and at this point much that Existentialism has to offer becomes useful in examining these choices. Sartre emphasized a "project", a set of goals and outside relations that each of us chooses to give meaning to our life. This emphasis seems well chosen to us after our examination of man's growing prefrontal lobes. More than any other animal, the human is a doer and a planner, and the emphasis on a long-term goal resonates with our biologic and intuitive sense of what gives meaning to a human life. To be satisfying, our future mythology will have to incorporate features of progress, of becoming, of providing a direction, to satisfy what appears to be an important human need.

Of course, this attempt to foresee our future values borrows much from the Existential confrontation with the anxiety of meaninglessness and the deliberate construction of human meaning. Yet important differences remain. We are looking for a biological basis for our value system, unlike the true Existentialist. We wish to predict our collective need for meaning, while the Existentialist struggle is intensely personal, with each seeker rearching his own independent solution. Further, the individual confrontation advocated by Sartre requires a great deal of individual courage, while the need for meaning springs up in many people who are not equal to the bleakness of the lone Existential quest. Each of us avoids a lot of painful introspection if we can choose to believe in a shared religion or mythology (provided it remains congruent with the remainder of our knowledge, including scientific knowledge). Today we are simply trying to predict some of the features of that necessary mythology.

We have already mentioned the so-called New Age notions, which try to fill the void of meaninglessness in modern life. Among these notions, I would like to mention the Gaia hypothesis as a mythology which seems to meet many of our criteria for an important vehicle of human meaning. Simply put, this hypothesis, first advanced by Lovelook, suggests that the entire biosphere of planet Earth is alive as a single super-organism, stating that tremendous corrective forces exist within our eco-system because

the eco-system itself is a single being with its own homeostatic mechanisms (fig. 9). This hypothesis is pseudo-scientific, sounding consistent with much of natural science, yet is conveniently untested on a scientific basis because of the vagueness of the concept. The emphasis on the environment is wholesome from an ecological standpoint, and provides a convenient framework for relating human individuals to a larger entity as grand as the living planet, yet as personal and nurturing as any Virgin Mary or Earth Mother figure. Lastly, the choice of a feminine deity may have important advantages in reducing aggression, and encouraging co-operation rather than competition among believers. Perhaps this would support a creative, nurturing stance rather than the conquering exploitive image fostered by Christianity and by many religions up until now.

In conclusion, a search for meaning must occur to fulfill important human needs, and an intelligent analysis of this need for meaning should precede any large-scale attempt to alter mankind's nature, whether through genetic or environmental manipulation. The Human Genome Project provide a useful symbol of our link to the objective world, causing the objective (natural sciences) and the subjective (philosophy and religion) to intersect at the point of our self-knowledge.

I would like to close with two images, a nightmare and a dream (fig. 10). The first is a cartoon showing our darkest fears regarding tampering with DNA and the nature of life. This theme of the destroying monster, often our own creation, dates at least from Frankenstein and recurs throughout science fiction to the



Figura 9

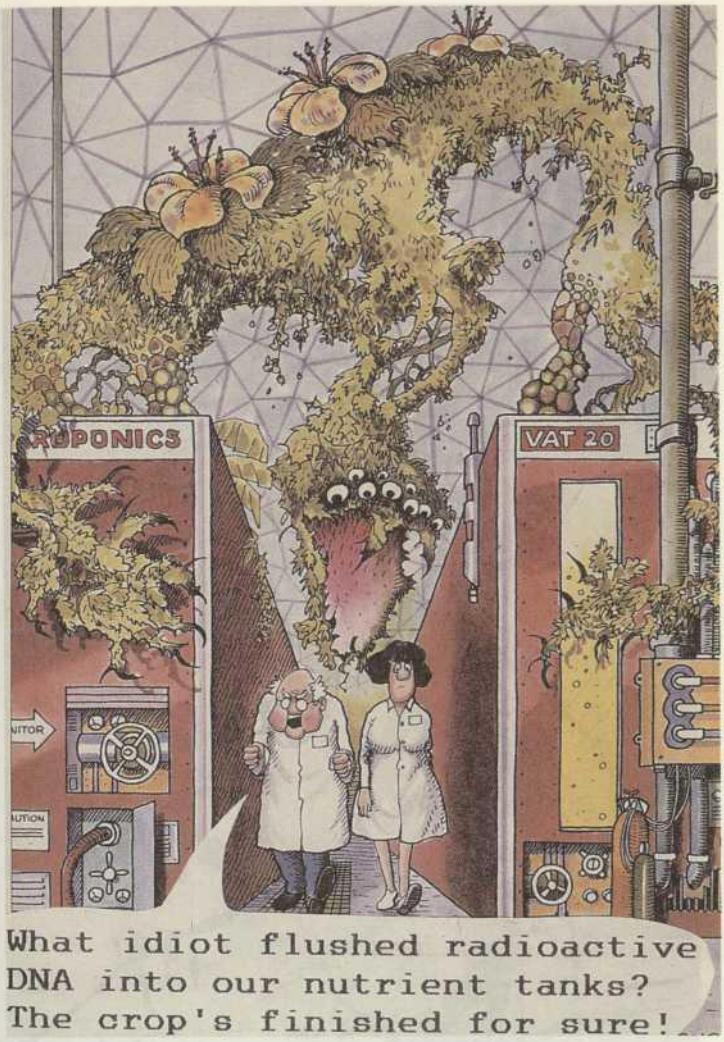


Figure 10

present day. I believe these monsters represent the artists' fears that in our technological society, objective science has triumphed over subjective human values, and that something essential about our humanity is placed in extreme peril, not by physical destruction but by reduction, by the daily moral erosion that accompanies a loss of value and of meaning.

In contrast, consider this Biblical metaphor (fig. 11). The double helix has sometimes been likened to Jacob's ladder, for example in this painting by Salvador Dalí. In the story of Jacob, he fell asleep and dreamed of a ladder ascending to Heaven. Thus Jacob's Ladder becomes the point of ascension, the intersection of the material, objetive world with the world of the spiritual, the

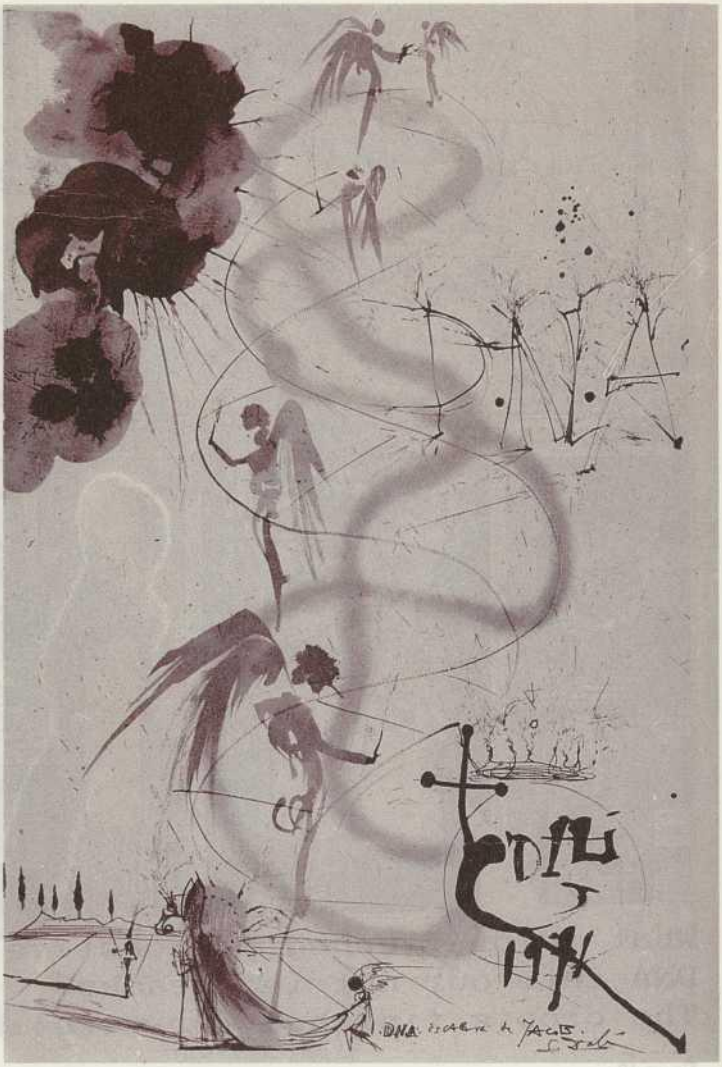


Figure 11

world of meaning. And this, precisely, is the metaphor I would like to leave in your right hemispheres, that we as scientists are climbing Jacob's Ladder by studying the Human Genome, and that the resultant self-knowledge will help us to reach the world of spiritual values, uniting it with the objective world of science.

THE IMPACT OF THE HUMAN GENOME PROJECT ON MEDICINE

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GENETIC THERAPY

Theodor Friedmann

Center for Molecular Genetics, School of Medicine. University of California, San Diego.
La Jolla, California (USA)

ABSTRACT

The Human Genome Project will bring new knowledge on the therapy of disorders with a high genetic component, although it is true that in general there is a certain delay between knowledge of human genetics and the clinical and therapeutic application of this knowledge. Although the project aims to discover the structure and function of the Human Genome, it is to be hoped that all this will be translated into therapeutic programmes. The history of medicine, as far as genetic disorders are concerned, shows that therapy has been directed at all places except at the root of the problem, that is, at the gene which causes the disorder. Today, genetic therapy is being used, especially in the somatic field. Genetic therapy in the germinal field is another matter for it aims at genetic and metabolic correction, not only in the patient but also in his/her descendants.
However, both therapeutic modalities pose ethical problems which will gradually change as our technological stockpile changes.

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However, both therapeutic modalities pose ethical problems which will gradually change as our technological stockpile changes.

Good morning. It's my pleasure to start the discussion this morning on the medical applications of some of the issues that we have been discussing. And it is my pleasure to introduce to you and review for you some of the aspects of one of the issues that has something to do with the Human Genome Project, but which is not necessarily intimately involved with it. I'd like to review for you some issues related to human gene therapy and its relation to the genome project. If one is looking for historical or literary equivalents of modern molecular genetics and the issues of gene therapy, one might think of things like "Great Expectations" or "The Age of Anxiety", or even the promises and exploits of El Cid. "The Age of Anxiety" is obviously the basis of some of the discussions that we are having. Genetics does pose problems for us. "Great Expectations" speaks for itself and reflects the hope, of course, that what we are doing will lead to enormously new and useful techniques for the human condition. We have heard and will continue to hear that genetics has a very special place in raising ethical issues, the issues dealing with the nature of man and the human condition, in general. The explosion in human genetics has come to remind us that genetic knowledge represents in one way a particularly liberating kind of knowledge for the promise of the relief of human suffering. It also promises, at the same time, to some of us a particularly threatening kind of knowledge with respect to the knowledge of ourselves as individuals and as a society. The vulnerability of genetics to mischievous and even evil application has been known for a long time, illustrated by the Birth of Eugenics movement in Britain in the nineteenth century, and its further perversion in the United States through the work of Charles Davenport and others at the Cold Spring Harbor Eugenics Record office. The work there led to misguided social policies, immigration policies and the sorts of disasters that we heard of yesterday from Doctor Smith, dealing with Carrie Buck and the compulsory sterilization laws in the United States. And, of course, the ultimate surrender of science reached its atrocious extreme in the evil public policies and programs of Nazi Germany and the Lysenko period in Russia. And we will hear more of that later in the program. This meeting is taking place because we intuit, we understand that there are problems with some of this genetic knowledge and with its application. Those problems are in the realm of science policy, in the uses and abuses of personal genetic information for screening and monitoring programs.

One of the expected and often stated expectations and promises of the genome project, of course, is the delivery of immense new knowledge of genetic disease and the translation of that into powerful new kinds of therapy for diseases with major genetic components. I think that we hall know that many of the first

and earliest deliveries of that promise will take the shape of effective screening and monitoring programs rather than therapeutic programs. There is always a very mayor and long hiatus between what we learn in genetics and how we apply it in the clinical and the therapeutic setting. I might just remind you that the case in point is that of hemoglobin and its disorders. There is no gene and no gene product as well understood as hemoglobin. Its molecular biology is as profoundly production are treated, even today, I think you will see the great discrepancy between the knowledge that we have of the disease and our ability to treat.

Well, what does all this have to do with the Human Genome Project. We heard yesterday from Norton Zinder that the genome project is not aimed entirely or even largely at understanding all of human biology and all of human medicine, but rather at the structure and function of the Human Genome. It is true that that is often translated into promises of therapy. I would like to describe to you in these few moments a bit of the state of the art of gene therapy, where it is and where it is likely to be going in the near future. I will then look at some of the problems and concentrate on two of the issues that I see to be of interest and worthy of further discussion by this group, and other groups.

Gene therapy is not a child of the Human Genome Project. It's been with us for some time and is an independent creature born of other parents. Although there is no question whatsoever that information gathered from the Human Genome Project will immensely catalyze the activities toward novel therapy. Well, in fact that, when the concept of gene therapy came to be a gleam in the eyes, some twenty years ago, it wasn't really possible to stand in a respectable scientific audience and utter those words and, I think, you will recognize an immense change since then, one that probably represents as epochal and as a major a change in medical thinking as has ever occurred in the historical of medicine. I'll try and convince you of that in the next few slides, that this change involves a 180 degree turn in the way we think about the treatment of disease. I can't see very well from here, but I think the first slide presents a very simplistic scheme of genetic disease. We all know that genetic disease reflects defects in the genetic material and that it results in the production of abnormal gene products –proteins, enzymes and other gene products. Normal gene products allow normal cell function and physiology. But when they are aberrant of mutant, cell or organ damage takes place and disease results. In all of medical history up to the present time, all therapies have been aimed everywhere except at the site of the defect. We have been able only to imagine treatment of diseases by manipulating the results of the metabolic and

physical consequences of genetic defects and biochemical defects. It has never been possible to imagine treating what really is the problem in the mutant gene.

One can imagine the gene to be a dam and a mutant gene to be a leak in the dam. That results in a flood downstream. This flood is disease. Medical therapy, in all its forms until now, has been a frantic effort to clean up the mess that occurs from this broken dam, and such an attempt at therapy becomes very ineffective and after a while the dam continues to leak. What is happening now –in a very simplistic view– is that we are now able to change the therapeutic approach into one that involves a repair of the defect, the broken dam. Attempts to treat disease by fixing the dam itself are now what I think of as an epochal change in medicine. The concept is "fix what's broken!" The gene is broken, so let's learn to fix the gene. Well, there are people who are, in fact, trying to do what. Many of the models involve removing cells from a patient, introducing foreign genes into then *in vitro*, then returning them to the patient into an appropriate site, or possibly, even using gene transferring techniques directly into the patient.

There are two principal kinds of target cells for this kind of manipulation –somatic cells and germ cells. Treatment of the somatic cells of the patient results in genetic correction of only the individual patient –hopefully a permanent treatment of that patient and only that patient. The other possible approach involves treatment of the germ cells of a patient, so that the genetic and metabolic correction and complementation of the defect becomes evident not only in the patient but in the progeny and future generations.

Many of you will recognize the somatic cell approach as the basis for the several proposals that have been approved now by the Recombinant Advisory Committee (RAC), NIH, and by the other regulatory agencies in the U.S. In one of those experiments, Anderson and his colleagues are removing lymphocytes from a child with Adenoise Deaminase (ADA) deficiency, introducing that gene into the lymphocytes of the patient and then returning the cells to the patient to try to provide permanent new ADA function. Another approved protocol in one in which tumor necrosis factor (TNF) genes are introduced into cells are returned to the patient. There are other models that people have been working on in our own laboratory –in an attempt to correct cancers that result from defects in cancer suppressor genes. Here is a retinoblastoma tumor cell that has been corrected by having a normal retinoblastoma gene introduced into it. These cells now become non-tumorigenic. The corrected cells are put into nude mice and

they are now re-expressing the RB gene product and are no longer able to produce tumors.

Similar approaches have been taken to correct disorders such as LDL receptor deficiency, with its resulting hypercholesterolemia. New genes can also be put into muscle cells. This is an approach to treatment of things like Duchenne's muscular dystrophy. So these promises would, at first glance, represent an unqualified good. But there are problems. We all recognize that we've run into ethical situations, dilemmas that were somewhat facetiously called "playing God", yesterday. In fact, "playing God: is another phrase for Medicine. The approach of the arrogance of the hubris of medicine in deciding that there are such things as mistakes in natural and our requirement, in fact, our injunction to correct those mistakes, is called the profession of medicine. Some of us regard this injunction to heal and cure an important defensible thing to do. Eric Lander described the place of changing technology in our changing ethical landscape. We've seen rather remarkable changes in gene therapy, stemming from the early fears and the disasters of the experiments of Martin Cline and Stanfield Rodgers before that.

We are now coming to a point where gene therapy is not only defensible but imminent and, in fact, taking place. There are two sets of problems that I would like to bring to your attention, problems that still remains in gene therapy. The first is the problem of somatic cell versus germ line therapy, an issue that I think has so far been poorly examined and too easily dismissed. I suggest to you that the level of the ethical discourse with respect to germ line therapy has been extremely poor, even though it is a problem that requires very careful and considered discussion. The second very difficul set of issues relates to contentious questions of "what is disease" and what are the targets at which we should be aiming our therapeutic armamentarium. Some phenotypes, such as Tay-Sachs disease, represent clear and obvious diseases, and most moral agents among us would agree that there is very little benefit and very little good to be derived from those kinds of human traits. But there are many human characteristics and other qualities, of intelligence and personality that do not necessarily represent diseases to be eliminated, but chareacteristics that may be deleterious, but that also may serve important and useful purposes. These too come under attack or become vulnerable or susceptible to modification. They are the kind of qualities that we may be able to modify but obviously should not until we are able to understand more about the long term consequences of these modifications. I think my time is up. I would like to end by reiterating for you the immense need for continued discussion, not only of the

technology, but of the impact of these manipulations. We have at least two major ethical problems that remain before us, but I think that even these problems will change as our technological armamentarium changes. Today's problems will disappear or modify in the future but I would like to suggest the Fundación para los Estudios Avanzados might consider the future meetings will concentrate on these.

THE IMPACT OF HUMAN GENOME MAPPING ON THE DOCTOR-PATIENT RELATIONSHIP

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ABSTRACT

Bearing in mind that the genetic map is as yet a non-fulfilled future, the author describes a probable discourse for this moment of the relationship between doctor and patient, which entails the following: a future illness will be experienced as a present reality; the potential will become the present; the interventionist, active medicine of today will change to become a comtemplative science; and the duration of the current doctor-patient relationship will give way to a doctor-community relationship.
The present limits to the doctor-relationship will be renewed and modified to the extent that the elaboration of a genetic map progresses.

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My role is to discuss the implications of mapping the human genome for the relationship between physicians and patients. Only a tiny fragment of the genome has yet been mapped and only a few human diseases have been linked to that small map. Thus, any implications for the relationship between patient and physician are speculative and probable. Allow me to make this speculative and probable topic concrete and visible through a meta phor: the metaphor of map making. This is, of course, the master metaphor for the entire scientific enterprise known loosely as The Genome Project. James Watson and Norton Zinder vividly employed the metaphor in a recent letter to the New York Times [Oct. 13, 1990, p. 14]: "Like the system of state highways spanning our country, the map of the Human Genome will be completed stretch by strech".

The scientific work of creating linkage maps and physical maps, whereby genes are assigned to chromosomes and their nucleotide sequence identifed is somewhat like, but not very much like, the drawing of squiggly lines within Mercator projections to designate coasts, islands, mountains, and the boundaries of political entities. Some of the products that issue from the decoding of the genome maps even look like geographical maps: low resolution physical maps made under light microscopy resemble to high resolution photographs made by remote sensing satellites such as this one of... taken from SpaceLab. High resolution genomic maps of E Coli or phage T4 look rather like the circular mappamundi of the Middle Age, such as this splendid Catalonian map that belonged to the Borgia family. Yet for the most part, the investigative methods, the physical materials and the biochemical references of genomic maps are quite unlike geographical maps and mapping. The interminable series of code letters and words that express sequences would never be mistakes for a roadmap. Still, the metaphor is a useful one-it makes concrete and visible a highly complex and elusive structure of matter.

The mapping metaphor is most appropriate to Spain, the site of this conference. In the 15th and 16th centuries, Spanish and Spanish-sponsored explorers touched far corners of the globe. Their explorations made new maps possible and made new methods of mapping necessary. The first modern Atlas was produced by Ortelius, geographer to Felipe Segundo. The art and science of mapping owes much to Spain (and to its neighbor, Portugal). By the middle of the 16th century, all the lines on the surface of the globe had been redrawn, new ones added and old ones rendered more accurate. The gradual discovery of the locus and sequence of the Human Genome will be like the European discovery of unknown lands: it will, among other

effects, require the redrawing of the lines that mark the present boundaries of the relationship between physicians and their patients. By the middle of the 21st century, the genomic physician and the genomic patient will look upon each other from quite different standpoints than they do today. Naturally, like territorial boundaries in remote areas, the boundaries of the patient-physician relationship as it has existed and as it will exist in the genomic era will often overlap. Some territories will remain in the old domain; many of the new features will resemble the old. Still, it is my contention that the map of the relationship will become a new one as the scientific work of mapping the genome proceeds. It is my intention to describe that future map, recalling, however, that since we describe an as yet unrealized future, my words are somewhat like the work of the medieval cartographers who drew maps of places they had not seen.

The map of the relation between physician and patient has been redrawn several times in the history of western medicine. The revision has been made necessary by new information, sometimes at the level of theory, sometimes due to new data, that has radically modified the way disease and healing were understood. The most recent revision came in the latter half of the 19th century. Prior to that era, physicians learned about their patient's illness primarily from the patient's own reporting of their symptoms and they linked those reports to ebbs and flows of internal fluids that themselves responsed to external, cosmic forces. In almost all ancient medical theory, the patient was a microcosm engulfed in the macrocosm. Interventions were designed to redress imbalances not only within, but between within and without. There existed no reliable way to link signs and symptoms to the malfunction of discrete organ systems.

In the 19th century, medical sciences became increasingly capable of relating the patient's signs and symptoms to an organically based pathology. The single disease of microcosmic imbalance fractured into multiple diseases sited in specific organs and caused by specific agents. The patient was no longer a microcosm but rather a site for disease processes. This required a redrawing of the map between patient and physician. In the former era, the physician stood before the patient as a listener, observer and counsellor. In the new age of physiological pathology, the physician gradually became an intervener, seeking out the organic or organismic source of disease and extirpating it. The new physician became able to enter the living body, first by stethoscopic auscultation, then by x-ray and all its radiological and endoscopic successors; the bodily cavities were physically entered by sterile,

painless surgery. As the physical boundaries were passed, the relational boundaries changed. I shall call the relational map that came about after the middle of the 19th century, the map of modern medicine.

The map took on the following configuration. It shows a patient presently suffering from an ailment presenting himself or herself to a physician who sets out to discover and extirpate the cause of the ailment. The relationship was established on the basis of an actual complaint at the present time, requiring active intervention for diagnosis and treatment and united two persons, the physician and the patient. Thus, the relationship could be described succinctly as an actual, present, active duality. Spain's great philosopher of medicine, the late Pedro Laín Entralgo, reflected on the structure of this relationship and defined it as "a quasi-diadic and helpful cooperation, whose purpose is that the patient should achieve the psychosomatic situation we calls health." [Doctor and Patient. Trans. Frances Partridge. New York: McGraw-Hill, 1968, p. 152]

There are, of course, many nuances in this description that we cannot explore: I refer you to Dr. Laín Entralgo's beautiful little book, *Doctor and Patient*, from which the above definition is drawn, for that exploration. My purpose is sketching the modern form of the relationship is precisely to suggest how the gradual revelation of genomic information will modify it, will redraw the boundaries of the relational map.

Genomic information will effect many changes in the ways in which we understand the biochemical basis of human development and of health and disease. Put in the most general way, genomic information will increase the specificity with which we can identify and predict the biochemical determinants of developmental and physiological normalcy and abnormality. The inevitable development of disease and the presence of risks for disease, as well as possibilities for prevention, cure and risk reduction will become much more visible and practical than ever before. This will bring major shifts in the lines than demarcate the relationship between physician and patient.

Before describing the new map itself, we must describe the paths that scientific exploration into the genome is taking. The speakers at this conference will relate those path in detail. Allow me to do so in rough outline and with reference to the possible clinical applicability of scientific discovery.

It appears that the first voyages of discovery into the genome will achieve the mapping and sequencing of many and ultimately all, of

those conditions known to be monogenic. This will expand the capacity for carrier screening and presymptomatic detection that we already have. Thus, the ethical issues that have appeared for Huntington's or polycystic kidney disease will appear for a broad range of late childhood or adult onset diseases, such as Fabry's Disease, retinitis pigmentosa, ocular albinism or adult onset muscular dystrophy. Prenatal diagnosis and presymptomatic detection will render clinically present many conditions, of varying severity, that would otherwise not be perceived, felt or experienced by the affected person for relatively long periods of time. This sort of genomic knowledge will precipitate the first shift in the patient-physician relationship.

The first shift will be from Present to Future, or more accurately, the drawing of the Future into the Present. In modern medicine, a person becomes a patient at the point when a present ailment manifests itself (I abstract from the broader sense of "patient" that covers the quasi-constractual relationships involved in finding and selecting someone to provide physician services when needed). People come to the doctor with a "presenting complaint". The activities of diagnosis and treatment are initiated in this way. Genomic information will signal future disease or desease risks. As the molecular basis for single-gene inheritance of common debilitating diseases unfolds, diagnosis and prognosis will collapse into each other. We already know that there are families in which breast cancer, colon cancer, Alzheimer's disease occurs in autosomal dominant fashion. Future disease will enter the patient physician relationship. Persons will become patient's before their time. They will be described in disease terms but "feel fine" and "be fine", for years, perhaps always. The future, however, will be made more vividly present than ever before.

A second shift will be very much like the first: not only will the Future become Present, but the Potential will become Actual. Modern medicine knows enough about "risk factors" to be able to inform patients with certain characteristic or life styles that they may become ill in the future. Classic genetics described the patterns of inheritance the constituted risk for disease or for transmission of disease. Still, the development of actual disease lay in the future and remained a probability, not only in the statistical but in the psychological sense. Genomic information will, at least for monogenetic Mendelian disorders, make than potentiality an actuality. Even though the illness has not yet appeared, it has been found biochemically present. In a similar way, the risks associated with multi-factorial disease will become much more palpable. Genomic information will identify an increasing number of genetic loci in which the presence of a specific DNA sequence, perhaps one of several variant sequences or alleles

found at that locus, is associated with increased risk for a condition, such as cardiovascular disease, cancer, diabetes, depression. Some of these conditions will be polygenic; other will require environmental and behavioral co-factors; in both cases, the number of these may be vast and their nature obscure. Still, persons can be designated patients in an anticipatory sense, as a schizophrenic or cardiac or cancer patient long before any illness is felt or any pathology damages the organism. Even though prediction of clinical manifestations in the individual will not be highly accurate, since it will derive from population data, still the reality of risk will be much more palpable. Today these risks are written in abstract numbers that have but remote impact on a person's perception of themselves; tomorrow they will be written in the genome, an indelible part of the self. As an anticipatory patient, they will watch themselves and physicians will watch them for the appearance of disease. This, of course, may be of benefit, should prevention or early treatment be possible. But, wheter beneficial or not, potential disease will become actual, as never before.

In theory, genomic information should provide not only the diagnostic and prognostic aspects of the patient-physician relationship. It should also point toward the therapeutic. We have many possible routes to prevention. We have already embarked upon gene therapy. We can glimpse ways in which genomic information can guide and enhance current pharmacotherapy. Still, the theoretical potential for therapy is not likely to be realized in any broad, much less universal way. Unquestionably, this has always been true of medicine: many diseases have been recognized and even well understood without the faintest hope of curing or changing their course. This became dramatically true in the mid-nineteenth century, when medical science tore the veil of ignorance between disease and organic pathology. So much became known about the causes of disease and so little was available to treat it effectively that "therapeutic nihilism" became the prevailing medical philosphy. Gradually, with the appearance of effective pharmaceuticals and efficient surgery, this nihilism was converted into a therapeutic activism. Even though many disorders defy medical intervention, intervention of some sort has become mandatory.

This suggests the third shift of boundaries on the map of the patient-physician relationship: a shift from a *Scientia Activa* to a *Scientia Contemplativa*. Modern medicine is predominantly a *Scientia Activa*, a collection of diagnostic and therapeutic actions that start in the logic of clinical judgement and terminate in interventions. Modern medicine reluctantly acknowledges the presence of untreatable disease, but assumes that at some time the

untreatable will e successfully treated. Genomic information, however, will announce the presence or the possibility of disease without the application of the logic of clinical judgement and for which therapeutic intervention may be unavailable. We have already seen this in one of modern genetics first clinical triumphs, siting the locus of Huntington's Disease. As the mapped genome opens up broad vistas of information, it will, in a strange sense, return to medicine's impotent past. Genomic information, while promising many means of cure and prevention will unravel before us many more threatening conditions that will long remain untreatable. Perhaps the ancient art of prognosis, of predicting the natural course of disease, inculcated by Hippocrates, will be the principle beneficiary of genomic information, at least for the forseeable future. This implies that the *Scientia Activa* may become a *Scientia Contemplativa*: many diseases will be understood more radically than ever before, but the disease course cannot be changed, at least with current knowledge, thus it can only be expected, watched and wondered about, by both patient and physician.

The fourth shift will be from Duality to Community. Modern medicine is, as Laín Entralgo expressed, a duality between a patient and a physician. He even wished to describe it as a species of *philia*, that is, friendship. Genomic information will push back the bounds of that duality into wider communities or populations. Genetic information by definition ties and individual into his or her heritage and to his or her heirs. The diseases linked to genetic loci flow through families from generation to generation. The individual who stands before his or her physician seeking information and help is, in the genetic view, an instance of a group linked together through social instituions such as marriage and heritage and through shared biochemical characteristics. We already see this in the techniques used to develop RFLP linkage maps: whole families and different generations must be drawn into the diagnostic process. We even see this in the termination of pregnancy following prenatal diagnosis: a potential heir is eliminated. We also can glimpse the presence of others, genetically unrelated, but intensely interested in the individual or family under investigation: insurers, employers, public health officials, police, government. Individual risk profiles will find their way into many computers and file drawers: the intrinsic difficulty of interpreting them accurately will be ignored as they become useful instruments for sorting out the fit from the weak, the safe from the dangerous, the cost-effective from the costly. More and more, a large population will stand around each patient, providing essential information, posing possibilities for prevention and seeking out previously private information for purposes of social or eco-

nomic utility. The duality of the modern relation between physician and patient will widen into a broad community. The Duality will become a Multitude.

This, then, is my new map of the patient physician relationship that will be drawn as the exploration of the Human Genome proceeds. The current map of a duality dealing actively with a present disorder will be redrawn to show a community contemplating a future disorder or probability thereof. Obviously, the old and the new maps overlap at many points: there are within the current repertoire of medicine situations which look much like the situations of the future. Obviously, as well, future situations will often be quite similar to the present. Yet, I am suggesting that a mjor shift will take place. The maps of the 16th century did sharpen many of the geographical boundaries: these were but minor shifts. Much more importantly, they revealed "theres" that had been previously unknown and showed how it was possible to get from here to there in previously unsuspected ways. These were the major shifts.

The mapping of the Human Genome, the, will require a remapping of the relationship between physician and patient. Unlike the mapping of the genome, which is a scientific voyage of discovery, the remapping of the relationship is a political adventure. It will require diplomacy and may result in revolutions in social institutions, legal provisions and economic arrangements. New claims of rights and duties will emerge. Above all, just as when political boundaries are redraw, loyalties and allegiences will be challenged. The bond that has tightly linked physician and patient for so many centuries will be stretched within the emerging network of the multitudes to whom genomic information is valuable. The traditional ethical features of the relationship will have to be redesigned in some respects and strengthened in others. My colleague, John Fletcher, has written sensitively of the ethical implications of genomic information for medical genetics. [Fletcher, J. C., Wertz, D. C. Ethics, law and medical genetics: after the human genome is mapped. *Emory Law Journal* 1990; 39: 747-808]. However, those implications go beyond the specialty we call medical genetics: genomic information will transform all medical practice into medical genetics.

I am sure that much of what I have said sounds rather negative. However, the shifts I have described are, like all major changes in social and institutional life, a mixture of positive and negative. Genomic information promises significant therapeutic possibilities, but we must not delude ourselves by believing that they will come quickly or that they will be universal. Similarly, the shifts from the highly interventional scientia activa to something more

like a scientia contemplativa may not be all bad, given the notable power of intervention to harm or to do nothing for the patient. Finally, the shift from duality to multitude might press modern medicine out of the excessive individualism that ignores social and community responsibilities. Each shift, like each discovery of new lands and each movement of peoples from an old world into a new, will bring a mix of benefits and burdens, goods and evils.

Again we recall the ships that sailed from Cádiz four centuries ago. Their voyages not only mapped the world, they inaugurated social, political and economic events that radically changed humankind's view of itself and nations' views of their destinies. The map of the new world was not drawn by Cristóbal Colón, Vasco Núñez de Balboa and Fernando Magellan: it was also drawn by the theologians, such as Francisco Vitoria and Bartolomeo de las Casas, who expounded, in academic and polemic terms, on the new ethical imperatives and responsibilities of rulers, settlers and explorers Some of those events were glorious. The discoveries that will lead to the mapping of the genome will have similar dramatic effects on our perception of our nature and our relantionships with each other.

We must proceed with these explorations but, as one of our fine clinical geneticists, Neil Holzmann has said, proceed with caution. If I may annotate his warning, I would recall a dictum of St. Thomas Aquinas, who said about caution, by which he meant not timidity but carefulness, "caution is required because human behavior is so complex that good and evil are inextricably mixed: the prudent man cannot avoid evil altogether, but he should be careful to avoid by foresight the common pitfalls so that as little harm as possible is done". This wise comment applies as well to the prudent scientist: as the secrets of the genome are unravelled, human good and evil will appear: let us avoid by foresight the common pitfalls so than more good than harm comes of this extraordinary effort to expand the boundaries of human knowledge. Let this final sketch by Goya and its motto, "even yet, I am learning", provide an image for the project: many of the scientists in this room will look like this ancient long before this project's implications for science and medicine will be exhausted.

THE IMPACT OF HUMAN GENOME STUDIES ON CLINICAL GENETICS

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ABSTRACT

On account of growth in the scale of the work involved, huge benefits are to be derived from the Human Genome Project; the speed and efficiency with which hereditary components of monogenic disorders are analysed will increase, as likewise accuracy of diagnosis; it will facilitate the etiological study of complex and polygenic disorders, and will clarify the role played by gene in processes such as cancer and self-immune illnesses.

On a long-term basis, the concept of molecular illness will be better understood, a great deal of the human metabolism and development biology will be explained, thus increasing possibilities for genic therapy.

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On a long-term basis, the concept of molecular illness will be better understood, a great deal of the human metabolism and development biology will be explained, thus increasing possibilities for gene therapy.

Genetics today impacts on agriculture, ecology, sociology, philosophy and law; but probably its greatest impact is in clinical genetics. The role of clinical genetics at medical centers increases with appeals from families who call looking for help. The increase parallels the increase in information: the entries in Mckusick's standard catalogue increased from about 1300 in 1966 to about 4600 currently (Mckusick, V.A. Mendelian Inheritance in Man. 8th ed. Baltimore, Johns Hopkins University Press, 1988). This enormous increase is most patent in academic environments at tertiary care centers, where the clinical geneticists are consultants in rare diseases. As a result, it has been suggested that medical schools may come to be known as genetics school.

It is notable than both because we can now manage low birth weight and because so many different rare diseases are known, the leading cause of infant death (20% of those who die in the first year) is birth defect/malformation (see, for example, Roberts, D.F., Chavez, J. Vouty, D.F.ZM. Stvh. Fid. Vhilf. 56:44-48 [1970]. A new-born has a 2 to 5% chance of having a major malformation syndrome (see Hall, J.G., Powers, E.K., McIlvaine, R.T. and Ean, V.H. Am. J. Med. Genet. 1:417-436 [1978] for an assessment of frequencies of chromosomal, single gene, and polygenic disorders). At a large medical centre, of the order of 1,000 patients are seen per year, with increases of the order of 30% year in recent year. The average time spent with a clinical genetics patient is in the range of 3 to 8 hours with most of it spent in counselling. This time is poorly compensated, compared to quick procedures like endoscopy of the throat, and clinical genetics is expensive, difficult specialty for a medical centre to sustain. This problem will not go away, and is a vital concern for the health systems of all countries.

The functions of a clinical geneticist have, however, remained largely the same: accurate diagnosis; the best therapy possible; management of associated problems; achieving reliable prognosis; and determining and discussing with patients/families the risk of recurrence and their options. Human genetics has been the substance of these activities; and the Human Genome Project will therefore be directly germane. I will discuss here the implications of the scale of genome analysis, the resulting difference that can be made by genome studies, and ways in which that difference can be translated into patient benefits.

Genome studies have not waited for the Human Genome Project to be of extraordinary importance for diagnostic activities. One of the most recent examples of the usefulness of new information coming from genome studies is the recent isolation

of the gene in which lesions lead to cystic fibrosis (Rommens, J.M. et al. Science 245, 1059-1065 [1990]). In this case 1/2500 births in certain populations have CF, with a current median survival age of 26 years. Since the gene is an autosomal recessive, there is 1/4 chance of occurrence in siblings on an affected individual. Using linked markers and linkage mapping in families, considerable progress has been achieved in diagnosis; but recombination always limited the accuracy of the inferred information. With the establishment that 70% of the CF patients have the 3 base pair phe508 deletion, direct-gene testing which is far more accurate is available for those families. (This can be done in general by oligo-mismatch hybridization, by the change in restriction enzyme sites, or by comparing that region of normal and patient DNAs by PCR-based techniques. At least two of these tests are current for CF, and can be carried out by chorionic villus biopsy [at 9 to 13 weeks] or amniocentesis [at 16 to 18 weeks]).

Such genome studies aid directly in prenatal diagnosis, the prime tool of the clinical geneticist. Diagnosis has many justifications; but perhaps the most important is the alleviation of anxiety. With the introduction of non-directive counselling to ensure that the family can make its own choices, diagnosis provides accurate information and also permits the preparation of appropriate care for affected infants, particularly in the period directly after birth. For a disease like the sex-linked Hunter's syndrome, children can die young, and support is needed from the start; and for cystic fibrosis, early diagnosis permits adequate preparations and care to be organized as soon as possible.

It is however, true that cystic fibrosis lesion –like so many other hereditary scourges of humanity– was found largely by the application of standard linkage mapping and molecular biology techniques. In fact, as the compilation of Dr. Mckusik shows, a real and increasing number of analyzed without the use or benefit of the Human Genome Project. Both the lesions in a number of hereditary maladies and in a number of cancers can now be detected by specific molecular probes; and it is a rare genetic disease which does not have several research groups attempting to fathom its basis at the molecular level. What difference is made by the current international effort to carry out systematic analysis of the genome, and to bring together groups like this one to discuss the extraordinary ethical issues that are entailed?

Major benefits of the Human Genome Project accrue by virtue of the increase in the scale of work. We are not talking simply

about an expansion of the number of groups active in the study of individual diseases; but rather about the investment up front of enough resources to facilitate disease gene studies in general.

To see the difference, consider that each laboratory which has determined a likely location for a gene by linkage mapping or other means must usually initiate a laborius search for the DNA that corresponds to that region of the genome. Only when that region of the DNA has been pieced together from a number of clones can the search for the disease gene continue full force. In contrast, suppose that an overall collection of cloned DNA has been assembled to cover much or all of the genome: any particular investigator would automatically have at his disposal the starting DNA for his region of interest, and could immediately get on with the work of particular interest.

As a rough estimate, the availabitity of such a resource of mapped DNA would shorten the search for a disease gene by up to 80%, with a sharp reduction in necessary effort and cost as well as time. The efficient expansion of large-scale genome work necessitates a corresponding development of new technology, which work synergistically to aid in the search for any individual gene. For example, I have been very impressed with the work at the Centre for Genetics in Medicine at the Washington University in St. Louis. Workers there have pioneered in the development of yeast artificial chromosomes as a cloning vector and mapping tool, and have already substantively accelerated the studies of the regions of DNA including the loci for Neurofibromatosis I, Wilms tumor, Huntington's disease, and polycystic kidney disease. I consider that a foretaste of what is to come as the Genome Project gets underway.

Similar considerations apply to current efforts in the Genome Project to increase the resolving power and coverage of the genetic linkages map (Donis-Keller, H. et al. Cell, 51:310-337, 1987). The linkage map remains the reliable way to bridge investigations from pedigree studies of the inheritance of a condition to responsible DNA; and its refinement could yield much closer localization of a disease gene before physical mapping starts.

One major impact of the Genome Project will thus be on the speed and efficiency with which hereditary components in disease can be analyzed, and in the resultant dependability of diagnosis: the risks to children, the risks for the next child, etc.

A second major impact is clear if one considers that the discussions thus far has turned on diseases caused by lesions in single

loci; but in fact, the expected impact of genome studies is even more extreme for the case of polygenic diseases. For those, including schizophrenia and the hereditary component of alcoholism, there may be 4 to 8 genes which have a major influence; and it seems intuitively obvious that global information about the genome -as detailed as possible- will facilitate such studies; and that the identification of a group of genes involved in the etiology of such complex conditions may be possible *only* if it can be based on extensive genome analysis. Once again, diagnosis can certainly be aided.

It may be worth noting that in a third major impact, the benefits of genome analysis are not limited to the role and nature of damaged genes. In particular, for the outcome of chronic and acute organic disease and infectious disease as well, the make-up of host defenses is critical. Already new technology associated with long-range yeast artificial chromosome-based mapping of the genome has produced a great deal of new information about the Major Histocompatibility Locus (Chaplin, D., and Bronson, S., work in progress); and comparable information about viral and bacterial resistance, antybody repertoires, etc. will not be far behind. In many of these cases, we are not discussing "affected" and "unaffected" genes; but variant constellations of genes than can have very different (positive or negative) effects for patients in specific instances. This type of information will be important in determining the range of genetic effects in the response to environmental challenges and to cancer, and in the causation of autoimmune and other systemic diseases.

In the longer term, of course, one expects a fourth and final impact on the Human Genome Project that is founded on the concept of molecular disease. It has been demonstrated many times that mutational analysis can yield considerable insight about structure/function of components of the body. In fact, it seems certain that much of human metabolism and developmental biology will be explicated by genome studies, and that the increased level of understanding will shift the weight of the value for genome studies from diagnosis to prevention or even gene therapy. Here current practice; but it is surely releveant that yeast artificial chromosomes have been isolated containing large human genes in intact form and with normal neighbouring sequences, and that these chromosomes can be expressed when transfected into mammalian cells. This provides a first step both toward understanding and toward conceivable correction of some genetic maladies. In this context, I have no special competence to comment on the ethical considerations that arise and are the focus

of discussion here; but I hope that as groundwork for those discussions, I have helped to further outline the expectation of what is scientifically possible based on the Human Genome Initiative.

THE IMPACT OF THE HUMAN GENOME PROJECT ON BIOLOGY

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THE HUMAN GENOME PROJECT: IN DEFENCE OF BASIC SCIENCE

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ABSTRACT

The Human Genome Project aims to map and sequence the human genome. However, the development of both these objectives will not mean absolute knowledge of human genetics. Mapping and sequencing the genome means acquiring knowledge, and knowledge, as such, is basic science. Nevertheless, this basic knowledge will shed light on new paths of research for specific aspects of the genome.

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The Human Genome Project aims to map and sequence the human genome. However, the development of both these objectives will not mean absolute knowledge of human genetics. Mapping and sequencing the genome means acquiring knowledge, and knowledge, as such, is basic science. Necessarily, this basic knowledge will shed light on new pools of research for specific aspects of the genome.

Although the Human Genome Project has barely taken off, it has been talked about so much over the past few years that at present, it probably is the most widely known project in Biology. As far as one can see, there are three major reasons for such popularity: (i) the *"largest biological project ever contemplated"* (as it is called in the advertising of Human Genome conferences) is most impressive; indeed, the project is supposed to lead to knowledge of the full sequence of the over 3 Gb (Gigabases, or billions of base pairs) of DNA that make up the Human Genome; (ii) it is a brute force approach; as such, it can be understood well beyond the narrow circle of the scientific community; (iii) the notion has been spread that, once the project is completed, everything will be know about man and his diseases. These points deserve some comments.

That the project is impressive has to be admitted even by its strongest opponents. Sequencing over 3 billion base pairs is, in fact, such a formidable task that it recently was put aside for five years, hoping that dramatic improvements in existing techniques will occur in the meantime. Therefore, for the next five years,. the Human Genome Project will basically be a mapping project.

As far as *physical mapping* is concerned, it is presently intended to put physical markers (recognizable sequences, like genes or anonymous single-copy sequences) at distances of 100 kb or so (1 kb, or kilobase, is one thousand base pairs) along the one metre thread of DNA which runs through the 22 autosomes (chromosomes 1 to 22) and the 2 sex chromosomes (X and Y) of the human karyotype. Putting on a map over 30,000 landmarks is still a huge task, requiring the collaborative work of many laboratories around the world. The technology for establishing the physical map is essentially available; moreover,a number of new techniques are likely to be developed in order to proceed at a faster pace. Basically, what is needed is a series of overlapping DNA segments, which may be cloned in a number of ways, as yeast artificial chromosomes (YACs), as cosmids, or as plasmid. Particular unique sequences will then be placed on these ordered arrays of segments.

Genetic mappiong is a much more laborious enterprise and its resolution (hopefully 1 centimorgan) will be about 10 times lower than that planned for the physical mapping.

The fact that the human genome project is a brute force approach raises the question as to whether intelligent approaches cannot be used to develop short cuts in order to attain important goals, such as gene localization. One should not forget that the Human Genome is formed of over 90% non-coding, intergenic sequences (considered as "junk DNA" by certain biologists),

and that there is a need to circumvent the problem of investing a lot of sequencing effort on those regions, at least in a first instance.

A number of statements have been made pushing the idea that knowledge of the primary structure of the Human Genome is equivalent to knowing everything about a human being. No notion could be more misleading, as will be seen from the following examples. We know the sequence of mitochondrial genomes from over 20 different species of eukaryotes. In spite of this, we do not yet understand many functional aspects of this small genome (16 kb in size in animal cells) and of its interaction with the nuclear genome. Likewise, we know a large number of sequenced viral genomes, and yet we are still very far from understanding many basic problems in virology. Such examples could be multiplied to include plasmids, as well as the genomes of chloroplasts. These remarks simply serve to stress the fact that the availability of a genome sequence is a necessary, yet far from sufficient, condition for understanding the underlying biological problems.

The points made in the previous two paragraphs suggest that we cannot hope to understand what we would like to about the Human Genome simply by knowing its map and, later on, its sequence, although such a knowledge will definitely expand the number of known human genes and clarify a number of genetic diseases. If the goal is understanding human genetics and the role of various genes in health and disease, the effort made on the Human Genome Project should be paralleled by a much larger one on the basic molecular genetics of man and other organisms.

What will be attempted here is to show that basic science is not only conducive to a deeper understanding of the Human Genome than biotechnology, but also to the development of new working hypotheses and experimental approaches having a direct impact on the strategies to follow and the priorities to choose in the Human Genome Project. This will be done by using, as an example, work carried out in the author's laboratory. But, first, let us discuss the history of the word genome and its meaning.

A brief history of the word genome

The word *genome* was coined in 1920 by Winkler (11 years after the word *gene* was created by Johanssen) to denote the sum total of the genes of an organism, but only began to spread several decades later, because for many years it was not found useful by either geneticists or cytogeneticists, the former being interested in genes, the latter in chromosomes.

In 1948, it was discovered that the amount of DNA per cell is the same in all diploid cell types of a given species from multicellular eukaryotes, whereas the amount is half in gametes. The constant amount of DNA in a haploid cell of a given species was called c-value, or genome size. The constancy of genome size within a species waas, however, accompained by large variations within orders, families and genera. Such variations were unlikely to be associated with differences in organismic complexity, nor with the presumed numbers of genes, so raising the c-value paradox. Moreover, the genome size of most eukaryotes obviously was in large excess relative to the likely numbers of genes. Neglecting polyploidy, which was the main factor in a number of cases, the c-value paradox and the large size of eukaryotic genomes were explained by two not mutually exclusive reasons: gene duplication, and the expansion contraction phenomena affecting intergenic sequences. Both explanations were correct. In the evolution of eukaryotic genomes, gene duplication is common, and intergenic sequences do contract and expand. Since intergenic sequences represent the vast majority of the genome of multicellular eukaryotes (as we said, over 90% in mammals), the expansion contraction phenomena are quantitatively by far the most important factor.

A much wider spreading of the word genome in the 1960s and 1970s was due to investigations on the sequence organization of eukaryotic genomes, using methods such as density gradient centrifugation and reassociation kinetics. These pioneering efforts were followed, after the advent of recombinant DNA technology, by an explosive development of molecular genetics. This expectedly led to an exponential increase in our knowledge of genes, from both prokaryotes and eukaryotes, including the unforeseen discovery of introns in the latter. More recently, the use of restriction enzymes cutting at rare sequences and the separation of large DNA fragments by pulsed field gel electrophoresis paved the way to long-range physical mapping, which became an indispensable adjunct to genetical mapping. While all these developments led to an increasing use of the word genome, what recently made it a household word was the Human Genome Project.

The meaning of the word genome

Over a lifetime of 70 years, the word genome has grown from total obscurity to enormous popularity. This success was not paralleled, however, by an increased understanding of the genome itself. Indeed, the genome still seems to be largely perceived as just the sum total of the genes of an organism (and of the intergenic sequences, if present, as in the case of eukaryotes). This view was called the bean bag model of the genome. According to

it the genome is just a collection of genes, which, in eukaryotes, are randomly scattered over the vast expanses of junk DNA, essentially formed by intergenic sequences.

Evidence from our laboratory, however, has shown that the genome is much more than that. Indeed, the genome is an integrated structural, functional and evolutionary system that obeys precise rules, which amount to a *genomic code*. This view arose from investigations on the compositional properties of vertebrate genomes. The tacit assumption for this work was that base composition is a very important property of the genome.

Although this approach was already extensively applied to the study of the mitochondrial genome of yeast and of other nuclear genomes, the discussion here will be centred on the vertebrate genome, lagerly using the Human Genome as an example.

Compositional patterns an the genome phenotype

DNA preparations from warm-blooded vertebrates (mammals and birds) are made up of large fragments (usually having a size around 100 kb) that can be separated into a number of families characterized by different GC levels (fig. 1). The fragments derive, by the unavoidable mechanical and enzymatic degradation that occurs during DNA preparation, from much longer segments (over 300 kb on average), that exhibit a remarkable compositional homogeneity and were, therefore, called *isochores* (for "equal regions").

The compositional distribution of large DNA fragments, which corresponds, by far and large, to the compositional distribution of isochores, defines a *compositional pattern*. In man, GC-poor DNA fragments from isochore families L1 and L2 (fig. 1) represent about two thirds of the genome; GC-rich DNA fragments from isochore families H1, H2, H3 (fig. 1) correspond to the remaining third. GC-poor and GC-rich isochores are interspersed with each other, as well as with the isochores corresponding to satellite (simple sequence) DNAs and clustered repeated genes (like ribosomal genes), to form a *mosaic genome*. The strong compositional compartmentalization of the Human Genome (and of the genome of warm-blooded vertebrates in general) is in sharp contrast with the weak compositional compartmentalization of the genome of cold-blooded vertebrates (see fig. 1), which is made up of isochores that cover a narrower GC range, and with the even narrower, unimodal compositional patterns of most invertebrates lower (unicellular) eukaryotes and prokaryotes.

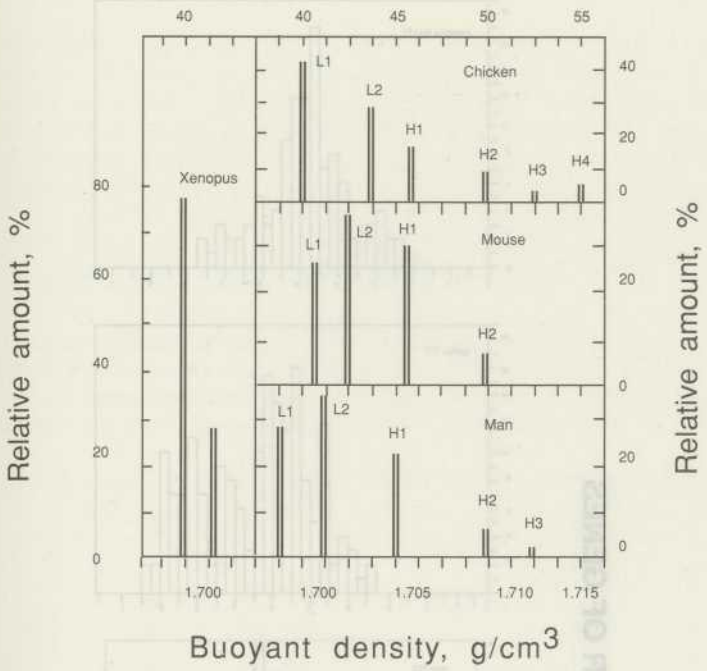


Figure 1.–Histograms showing the relative amounts, modal bouyant densities in CsCl and GC levels of the major DNA components from Xenopus, chicken, mouse and man. Major DNA components consist of DNA fractions, obtained by density gradient centrifugation in the presence of sequence-specific ligands, which are pooled according to their modal bouyant density in CsCl. Major DNA components derive from corresponding isochore families. The CsCl profiles of the major components are centered on their modal bouyant densities, but overlap with each other to some extent, particularly in the case of the components that are most abundant and closer in density. Satellite and minor (e. g. ribosomal DNA) components are not shown (From Bernardi, 1989).

Other compositional patters are represented by the compositional distributions of exons (or of their individual codon positions) and introns. In the genome of warm-blooded vertebrates, the compositional distribution of exons is skewed towards high GC values (fig. 2), in contrast with that of DNA fragments which is skewed towards low GC values (fig. 1). By contrast, genes (as well as large DNA fragments; see above and fig. 1) from cold-blooded vertebrates exhibit a more symmetrical and narrower compositional distribution (fig. 2).

The compositional patterns corresponding to the compositional distributions (figs. 1 and 2) of large DNA fragments (or of isochores), of exons (or of individual codon positions), and introns define, in fact, *genome phenotypes*.

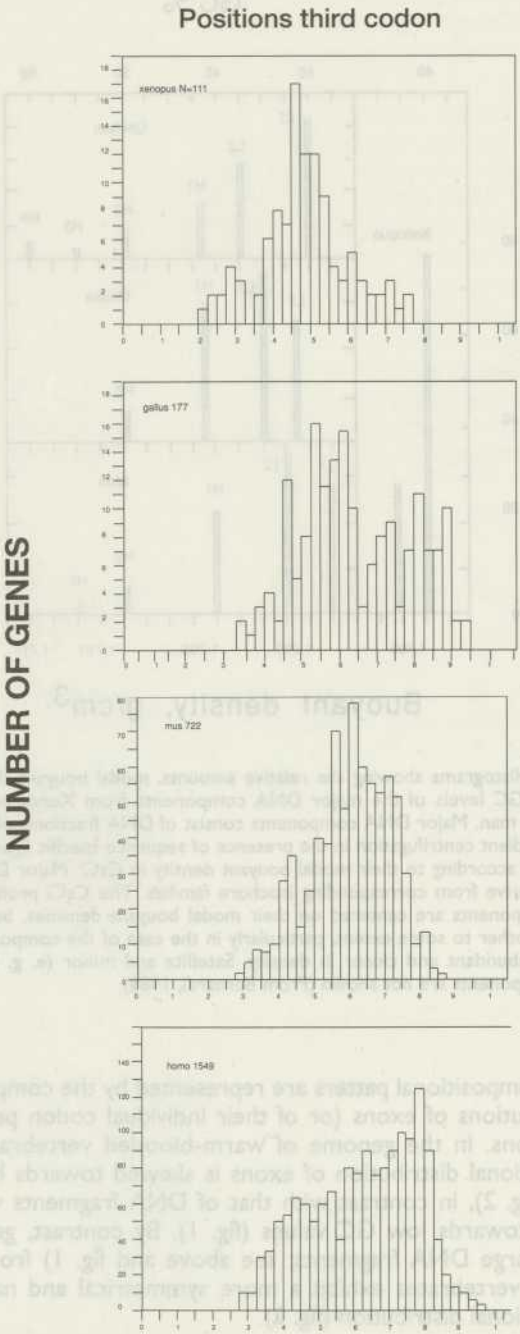


Figure 2.–Compositional distribution of third codon positions from vertebrate genes. (This distribution is the most informative because of its wider spread in composition compared to coding sequences and first or second codon positions.) The number of genes under consideration is indicated. The broken line at 60 % GC is shown to provide a reference (Modified from Bernardi, 1989).

The physical separation of large DNA fragments characterized by different GC levels, provided an opportunity to localize genes, or other sequences, in different isochore families by hybridization of appropriate probes. In turn, this led to the discovery that gene distribution is strikingly non-uniform in the human genome, the highest gene concentration being found in the GC-richest isochores, the H3 family, which represents less than 5% of the genome. The gene concentration in the H3 family can be estimated as at least 15 times higher than that in the L1 and L2 families.

A second discovery associated with the localization of genes in DNA fractions was that the GC levels of exons and introns are linearly correlated with the GC levels of the DNA fragments in which the corresponding genes are embedded (fig. 3). Since

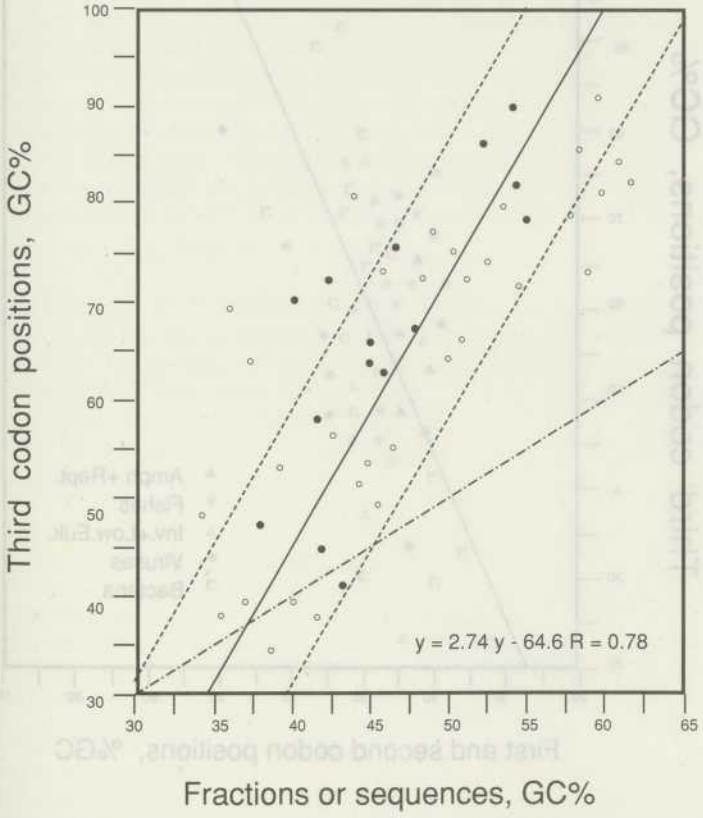


Figure 3.–Plot of GC levels of human coding sequences against the GC levels of DNA fractions or of extended, sequenced, DNA segments in which they were localized (From Mouchiroud D., Aïssani B., D'Onofrio G., Macaya G., Gautier C., Bernardi G., 1991, *Gene*, in press).

DNA fragments are made by more than 90% intergenic sequences, the relationship links, in fact, coding and intergenic sequences. Correlations basically similar to those described for man apply to all vertebrates, whereas in the case of plants, the basic features are the same, but with quantitative differences.

In conclusion, the compositional correlations just discussed are very general, since they concern whole classes of living organisms, although not universal. By contrast, the correlation that links the three codon positions of all genomes (fig. 4) is a universal one. The correlations between genes and isochores and those among codon positions amount to a *genomic code*. It should be stressed that compositional pattern (or the genome phenotype and compositional correlations (or the genomic code) are due to *compositional constraints,* acting on both coding and non-coding sequences of the genome.

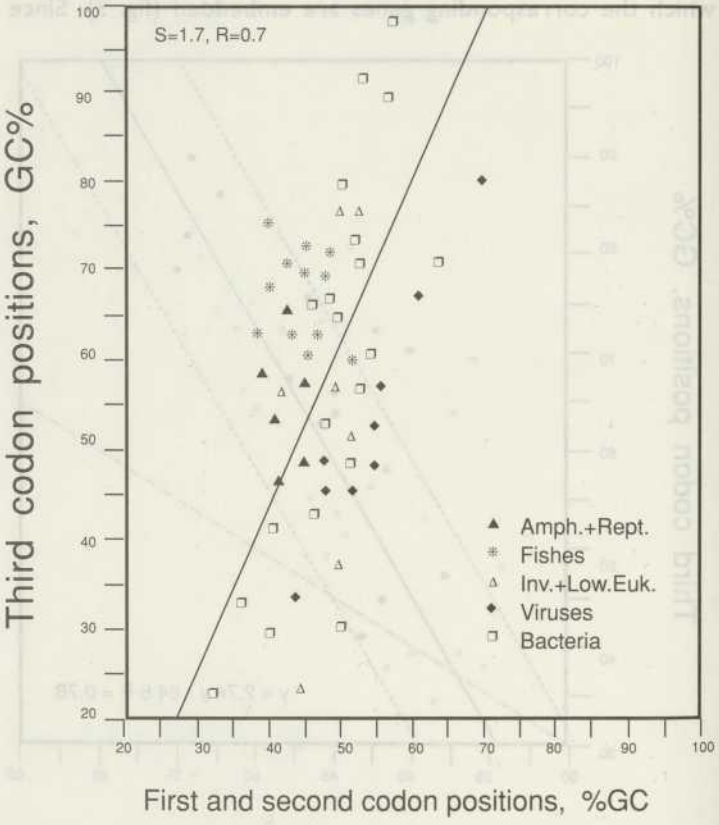


Figure 4.–Plot of GC levels of third codon positions from genes of cold-blooded vertebrates, invertebrates, lower eukaryotes, viruses and bacteria against GC levels of first + second codon positions (stands for slope and R for the correlation coefficient). The last square line obtained is practically coincident with that obtained for human and bacterial genes (From Bernardi G., Bernardi G., 1991, J. *Mol. Evol.*, in press).

Isochores, chromosomal bands and compositional mapping

Isochores are correlated with chromosomal G-bands (Giemsa positive or Giemsa-dark bands; these are equivalent to Q-bands or Quinacrine bands) and R-bands (Reverse bands; equivalent to Giemsa-negative or Giemsa-light bands). These bands are produced by treating metaphase chromosomes with fluorescent dyes proteases or denaturing agents, GC-poor and GC-rich isochores largely correspond to the DNA of G- and R-bands respectively, as indicated by the properties that they share (see table 1). G- and R-bands represent, therefore, a compositional pattern basically corresponding to the isochore pattern. It should be stressed that, in contrast to warm-blooded vertebrates, cold-blooded vertebrates are characterized by a poorness or absence of distinct G- and R- bands, reflecting the lower compositional compartmentalization of their genomes.

A more detailed understanding of the correlations between isochore patterns and chromosomal banding patterns can be gained through a novel approach: *compositional mapping*. Whenever long-range physical maps are available, compositional maps can be constructed by assessing GC levels around landmarks that can be probed. This simply requires the hybridization of the probes on DNA fractionated according to base composition and leads to the assessment of GC levels of DNA segments 200 kb or so in size around the sequence probed.

This approach, as applied to the long arm of human chromosome 21 (see fig. 5), has provided a direct demonstration for the remarkable compositional homogeneity of G-bands and for the compositional heterogeneity of R-bands. The latter are known to correspond to different families of GC-rich isochores and also to comprise a large number of thin G-bands only visible at high resolution.

Table 1: The Human Genome (a)

The Paleogenome **(G-bands, GC-poor isochores)**	***The Neogenome*** **(R-bands, GC-rich isochores)**
Scarcity of genes	Abundance of genes (esp. in H3)
GC-poor genes	GC-rich genes
Scarcity of CpG islands	Abundance of CpG islands
TATA box promotors	G/C box promotors
Less frequent homogeneity	Compositional heterogeneity
Late replication	Early replication

(a) Modified from Bernardi (1989); see this reference for additional details.

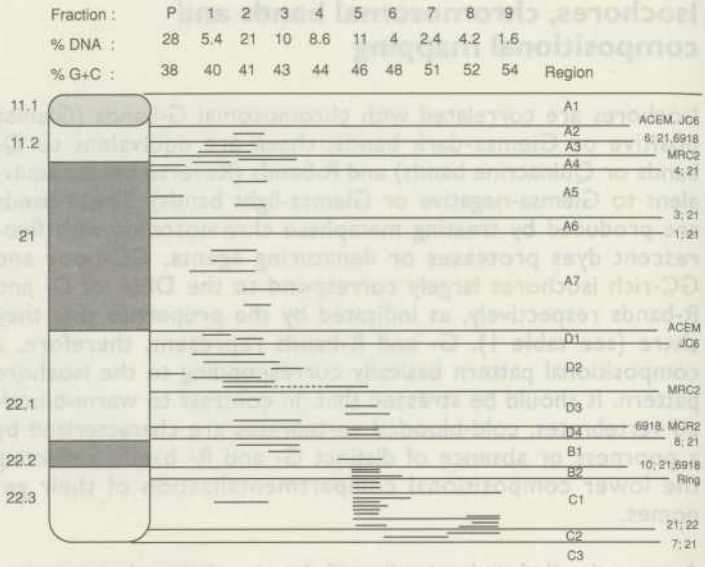


Figure 5.–Compositional map of the long arm of human chromosome 21. Long horizon tal lines indicate positions of the breakpoints defining chromosome segments. Short horizontal bars indicate the DNA fractions in which sequences from given chromosomal segments hybridized. This provides information on the composition of DNA segments 0.2-0.3 Mb (Megabases, millions of base pairs) in size (From Gardiner K., Aissani B., Bernardi G., 1990, EMBO J. 9, 1853-1858).

Compositional mapping has also shown that the GC-richest isochores of the long arm of chromosome 21, which has the highest gene concentration, are located in the telomeric region. In fact, telomeres almost always correspond to R-bands, and the terminal region of about half of them (including that of the long arm of chromosome 21) are the most denaturation-resistant regions of human chromosomes. We have suggested, therefore, that the GC-richest isochores correspond to such telomeric regions, a point already supported by preliminary results.

The compositional mapping of human chromosome 21, carried out as it was with only 50 probes targeted at loci scattered over about 40 Mb (megabases or millions of base pairs) of DNA, can only be considered as preliminary work. As more detailed compositional maps become available, they should provide the best high-resolution banding maps of chromosomes, without the uncertainties of cytogenetics.

Isochores and genome functions

Although we are only beginning to understand the functional relevance of isochores, some important points are already estab-

lished: (i) Integrated mobile and viral sequences are preferentially located in compositionally matching isochores; (ii) translocations, sister chromatid exchanges, chromosomal abnormalities, hotspots for mitotic chiasmata and fragile sites are preferentially located at G/R band borders and within R bands, namely at compositional discontinuities; (iii) GC levels of isochores largely determine codon usage (the differential usage of synonymouys codons) and the preferential utilization of half of the aminoacids (those only haing G/C or A/T in first and second codon positions); (iv) CpG doublets, the only potential sites of DNA methylation, and "CpG islands" (sequences which comprise G/C-rich promotors), increase from GC-poor to GC-rich isochores; (v) GC-rich isochores and R-bands replicate early and condense late in the cell cycle; the opposite is true for GC-poor isochores and G-bands.

Isochores and genome evolution

The compositional patterns of vertebrates define two modes in genome evolution. In the *conservative mode*, which is predominant in mammals and birds, mutations accumulate without causing almost any compositional changes in the genome. This can be seen by investigating the compositional distribution of DNA fragments and the chromosomal banding patterns, or, in the most rigorous way, by comparing homologous coding sequences. For instance, in phylogenetically distant mammals, homologous coding sequences do not show compositional changes, not only in first and second, but also in third codon positions.

By contrast, in the *transitional mode* large compositional changes take place, independently of geological time and sometimes over short time intervals. Two independent, major compositional transitions occurred in vertebrate genomes, between now extinct reptiles (therapsids) and mammals about 200 million years ago, and between other extinct reptiles (dinosaurs) and birds about 150 million years ago. These transitions are evident when looking at the compositional distribution of DNA fragments (fig. 1), and of coding sequences (fig. 2), including homologous coding sequences, and also at chromosomal bands. Indeed, these transitions led to the formation of a new compositional compartment in the genomes of warm-blooded vertebrates, the *neogenome* (see table 1). In this compartment, the ancestral, GC-poor isochores were changed into GC-rich isochores that contain abundant GC-rich genes, very frequently associated with "CpG islands". By contrast, the other compartment of the genome of warm-blooded vertebrates, the *paleogenome* (see table 1), is characterized by its similarity to what it was, and still is, in cold-blooded vertebrates. The GC-poor isochores contain relatively sparse GC-poor genes that are only rarely accompained by "CpG islands".

The findings obtained in our laboratory were presented here in order to stress two points.

The first is that basic science can go faster and deeper than any brute force approach, if the goal is to push our knowledge further. A whole series of new important concepts have been developed during the investigations discussed here: *compositional contraints* act on both coding and non-coding sequences of the eukaryotic genome and lead to the formation of *compositional patterns* (corresponding to a *genome phenotype*) and to *compositional correlations* (corresponding to a *genomic code*) between coding and non-coding sequences, as well as among codon positions.Compositional patterns at the DNA level have a counterpart at the *chromosomal level*, GC-poor, GC-rich and GC-richest isochores corresponding to the DNA segments present in G-, R- and T-bands. The *functional significance* of isochores is mainly stressed by the distribution of genes which are scare in GC-poor isochores, intermediate in frequency in GC-rich isochores, very abundant in the GC-richest isochores, and by the fact that both codon usage and aminoacid composition change in genes present in these three compositional compartments of the genome. From the evolutionary viewpoint, two modes of genome evolution have been recognized: the *conservative mode* in which nucleotide changes occur without any concomitant compositional change, and the *transitional mode*, in wich nucleotide changes are accompanied by compositional changes. The conservative mode predominates in the genome of warm-blooded vertebrates which show similar compositional patterns. The transitional mode was at work at the time warm-blooded vertebrates evolved from cold-blooded vertebrates and is rather widespread in cold-blooded vertebrates.

The secondpoints is that, in spite of the fact that no goal other than furthering our knowledge motivated our work, the basic findings just outlined have led to notions which are extremely important for the Human Genome Project: a) gene concentration in the genome is characterized by a compositional gradient; genes are at least 15 times more frequent in the GC-richest isochores which represent less than 5% of the genome than in the GC-poor isochores which represent over 60% of the genome; this puts a high priority on mapping and sequencing of the GC-richest isochores which appear to be located in T-bands of metaphase chromosomes; b) compositional mapping defines the compositional pattern that DNA follows along the chromosome; as such it identifies, much better than cytogenetics can do, the ultimate banding pattern of chromosomes and pins down the regions characterized by the highest gene concentrations.

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NO TIME FOR KNITTING: THE GENETIC QUEST OF THE ARGENTINIAN GRANDMOTHERS

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ABSTRACT

A blood relationship can be specified by means of a genetic test that entails the mythocondrial ADN. This kind of tests have been carried out in Argentina in order for their families to recover newborn children who had been kidnapped or had disappeared between 1976 and 1983. The human mythocondrial ADN is inherited through the mother and has been totally sequenced. Consequently, it is particularly useful when it is a question of establishing an individual's maternal blood relationships. The technique consists of the analysis of this ADNmt by means of restriction enzymes or by the chain-reaction by polymerasa (PCR). All this is just one instance of the usefulness and use of genetic information.

NO TIME FOR KNITTING: THE GENETIC QUEST OF THE ARGENTINIAN GRANDMOTHERS

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ABSTRACT

A blood relationship can be specified by means of a genetic test that entails the mitochondrial ADN. This kind of tests have been carried out in Argentina in order for their families to recover newborn children who had been kidnapped or had disappeared between 1976 and 1983. The human mitochondrial ADN is inherited through the mother and has been totally sequenced. Consequently, it is particularly useful when it is a question of establishing an individual's maternal blood relationships. The technique consists of the analysis of this ADNmt by means of restriction enzymes or by the chain-reaction by polymerase (PCR). All this is just one instance of the usefulness and use of genetic information.

Between March 1976 and December 1983, the Republic of Argentina was controlled by a series of military juntas that abducted, tortured, and murdered thousands o citizens (Amnesty International 1980; Interamerican Commision on Human Rights 1980). The military government ultimately fell following their defeat in the Malvinas-Palklands War. The total number of victims of extrajudicial execution will probably never be known, but in December 1983, the newly-elected democratic govenment established the National Commission on the Disappearance of Persons (CONADEP), with the request that this commission document, insofar as possible, the history of disappearances of citizens during the period of military rule. By September 1984, CONADEP had prepared evidence on 8800 victims. CONADEP and human rights organizaction believe the actual number of "disappeared" persons to be much higher (National Commission on Disappeared Persons, 1984).

We have been involved in helping to identify a special subset of these victims. These are the 210 children who were kidnapped at birth or as infants by military and police who murdered their parents and retained or sold the children. Unlike the older victims of the "Dirty War", many of these very young children remained alive, but were made to "disappear" (Abuelas de Plaza de Mayo, 1985). In 1977, during the period of military rule, the surviving relatives of kidnapped children formed the Grandmothers of the Plaza de Mayo, a human rights group devoted to finding kidnapped children and reuniting families. Through persistent collection and follow-up of circumstantial evidence, the Grandmothers began to locate their kidnapped grandchildren, primarily in the households of military and police officials and their collaborators (Nosiglia 1985).

It soon became apparent to the Grandmothers that it wa necessary, but no sufficient, to establish that a specific child was a kidnap victim. It was also necessary to establish each child's true identify by objective means. After the fall of the military and the election of a democratic government, it became possible to bring charges in Argentinian courts against the kidnappers of the children. The Grandmothers therefore asked geneticists for help in establishing objectivily the identities of these grandchildren. In June 1984, at the request of the Grandmothers of the Plaza de Mayo and CONADEP, we first travelled to Buenos Aires to help devoted procedures for genetic identification of kidnapped children.

In 1984, genetic relationships were most effectively established using serological testing of HLA antigens at the A, B, C; and DR loci (Albert et al. 1984). The inmunogenetics laboratory of Ana Maria DiLonardo at the Durand Hospital in Buenos Aires,

which was experienced in HLA serologic typing, agreed to undertake the identification project. That laboratory has been successful in establishing the identities of a large number of children and in presenting evidence to the Argentinian courts that has led to the reunification of families (DiLonardo et al. 1984; Diamond 1987).

In the intervening six years, we have extended the genetic approaches applied to establishing the identity of these kidnapped children. Two developments motivated this work. First, at the request of the Grandmothers and other human rights organizations, in 1985 the government of Argentina established the National Genetic Data Bank. This voluntary service offers grandparents, aunts, uncles, cousins, and other suviving relatives of disappeared children the opportunity to have their blood sampled, HLA serology determined, and white cells stored for extraction of DNA. Pedigrees documenting the relationships of surviving relatives to the murdered parents and missing children are also constructed. The intent of the legislation is that as children are discovered who are kidnap victims, their identities can be determined by matching to child to surviving relatives. Several hundred surviving relatives have contributed to the Data Bank in the past five years. Consequently, as kidnap victims are found for whom little circumstantial evidence of identity exists, each must be matched against multiple families. To establish identity with a sufficiently high level of statistical certainty under these circumstances usually requires matching to more than one genetic linkage group.

The second development during the project has been the appearance of families with few surviving relatives: deaths during the military period, fear on the part of some survivors, and subsequent deaths from natural causes have all taken their toll. It is no uncommom for a family searching for a missing child to include only the maternal lineage, sometimes only the mother or a sister or brother of the murdered mother of a kidnap victim. Therefore, it has been necessary to develop a genetic approach that permits the identity of a child to be determined even if only a single maternal relative is alive. We have appplied the sequencing of mitochondrial DNA to this task (New Scientist 1989; Orrego et al. 1988).

Mitochondrial DNA (mtDNA) as a genetic system for testing relationship

A wide variety of human sequences will undoubtedly be used eventually to test whether two individuals are related. We chose

mtDNA for this project for several reasons. MtDNA is haploid, maternally inherited (Giles et al. 1980; Hecht et al. 1984), and homoplastic within individuals (Wilson et al. 1985; Kocher et al. 1989). Therefore, each individual has exactly the same mtDNA as his siblings, maternal aunts and uncles, maternal grandmother, cousins via the mother's sisters, and so on, as illustrated in Figure 1. Second, human mtDNA has been completely sequenced (Anderson et al. 1981). Third, human mtDNA has evolved more rapidly than nuclear DNA and is extremely variable among individuals. This diversity has enabled the construction of evolutionary trees for humans based on restriction enzyme analysis of mtDNA (Cann et al. 1984; Wilson et al. 1985; Cann et al. 1987; Wilson et al. 1987). Finally, the introduction of the polymerase chain reaction, or PCR, greatly simplified sequence analysis by eliminating the need to chain reaction, or PCR, greatly simplified sequence analysis by eliminating the need to clone the target DNA in order to generate sufficient DNA for sequencing (Scharf et al. 1986; Mullis and Paloona 1987; Gyllensten 1989).

The control region of mtDNA, near the origin of replication, is particularly diverse among individuals. The mtDNA control region (also called the displace ment or D-loop) is a region of 1200 base pairs flanked by tRNA (Pro) and tRNA (Phe) genes. The control region does not code for any genes, which perhaps has released it from strict nucleotide conservation. In the control region, blocks of sequences conserved among mammalian species are separated by regions of high sequence diversity (Anderson et al. 1981). Obviously, mtDNA sequences will serve to identify the maternal leneages differ in sequence in the target region. Therefore it is crucial to be able to determine the probability that unrelated individuals would be identical by chance alone. We have compared hypervariable portions of the mtDNA control region from 14 unrelated Caucasian individuals (Anderson et al. 1981; Aquadro and Greenberg 1983; Greenberg et al. 1983; Orrego and King 1990). Of the 347 nucleotide sites compared, 32 were variable. When the sequences were compared between individuals in pairs, the number of differences ranged from one to 13 nucleotides; the average pairwise difference was 5.9 nucleotides. For these 347 base pairs, the probability that two unrelated individuals would be indentical by chance is approximately one in 370 (Orrego and King 1990). Therefore, this sequence of mtDNA could contribute to identification of maternal lineages. By sequencing more of the mtDNA control region, we can improve the statistical power of identification.

In order to test whether hypervariable sequences of the mtDNA control region are indeed conserved in human families, and in order to confirm the maternal inheritance of mtDNA, we selected DNA samples from three unrelated Caucasian children and the undisputed maternal grandmother of each. The six samples were am-

plified and sequenced without labels indicating who was related to whom. Matching children to their grandmothers was unambiguous.

Testing relationships in Argentina

As the result of the efforts of the Grnadmothers, 48 of the 210 children known to have been kidnapped at birth or in infancy have been identified, 12 identifications are now in progress, and 150 children are not yet found. Some of these cases will be discussed in detail at the symposium Meanwhile, blood samples continue to be collected from the hundreds of surviving relatives who are searching for kidnapped children. These blood samples are frozen in Buenos Aires, then sent to us for DNA extraction and mtDNA sequence analysis.

The major concern underlying this work is to do what is best for the children (Abuelas de Plaza de Mayo 1984). Clearly, circumstances vary enormously and the custody of each child must be decided individually. A few of the children born in captivity or kidnapped as infants were adopted in food faith by families with no ties to the military. The resolutions of these exceptional cases have generally been amicable, with the children being told the truth about their biological parents and spendig time with both their biological and adoptive families. However, the cases of children living with military or police officers involved in the torture and murder of their parents are far more dificult. These have comprised the vast majority of children discovered so far. Certainly under normal circumstances, a child would not be left with kidnappers or their accomplices regardiess of his age at abduction. The notion of assessing whether persons involved in kidnapping, torture, or murder are suitable parents for the children of their victims appears highly unlikely.

Kidnapping has universally been cosidered a crime. Is the situation different in Argentina because kidnapping occurred on a large scale? The human rights groups with whom we work suggest that to abandon the search for the kidnapped children of Argentina is to abandon a group of children who will not grow up in carefree innocence. As these children become adults, what would be their attitude toward relatives who knew they had disappeared but did nothing? What would be the effect on a young person to learn he has lived with people involved in the murders of his parents and that his surviving relatives did nothing to find him? Would failing to attempt to identify the kidnapped children implicitly grant immunity to kidnappers? Would this increase the sense of invulnerability of abusers of human rights in other countries? The historical situation that led to this application of genetics to human rights is unprecedented. Thus, answers to

these questions of ethics, law, and mental health are developing with our current experience.

As of this time (fall 1990), the political situation in Argentina is much more hostile to the Grandmothers' efforts than during the Alfonsin presidency of 1984-1989.

In particular, it is increasingly difficult to work within the Argentinian judicial system. However, the Grandmothers remain undaunted. They point out that the average age of the kidnapped children is now 15 years. Very soon, these children will have the legal right to determine for themselves their identities. For this purpose, mtDNA sequences will be available. Even though the grandparents of a kidnapping victim may die before the grandchild is found, the young adult's maternal lineage will be identifiable using the genetic information the Grandmothers have left behind. A young person can thereby be put in touch with his family –his surviving aunts, uncles, and cousins– and his history. For the past 13 years, the Grandmothers have been searching for their kidnapped grandchildren. Very soon, these grandchildren will come looking for them.

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PARTICIPATION IN AND ACCESS TO THE DATA OF THE HUMAN GENOME PROJECT

Elke Jordan

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ABSTRACT

The Human Genome Project is a biological research project with certain specific aspects derived from the scope of its aim, it is precisely this broad scope that justifies the need for diverse working or research groups to participate in it.

The participation of diverse scientists in a common aim means the production of numerous data that should be made available to all the scientific community participating in the project.

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The participation of diverse scientists in a common aim means the production of numerous data that should be made available to all the scientific community participating in the project.

Human Genome Project advocates have emphasized the importance of rapid sharing of resources and results as an integral part of this project. Without sharing of resources among genome researchers, the project will be inefficient and will take too long and cost too much. Sharing with others is also stressed because the results are too important to remain in the hands of a few. I would like to discuss here why both sharing among genome investigators and sharing with others are crucial to the success of the Human Genome Project.

Although sharing results as rapidly as possible is intuitively "a good thing" and a behavior that we value, it has not been insisted on in other fields of biological research to the extent that it has been promoted vis á vis the Human Genome Project. In order to understand why this is so, several questions need to be addressed:

- How does the Human Genome Project differ from biological science in general?
- How do these differences relate to the issue of sharing?
- What are the pros and cons of sharing?

In discussing these questions, I have a very practical objective. I am the manager of a large genome grants program at the National Institutes of Health, confronted with the need to set policies that will help and not hinder the Human Genome Project. I find myself at the center of a great deal of discussion of issues of sharing and in receipt of advice from individuals with opposing interests. I need to deal with the question –what is optimal sharing both within the genome community and with others? At this time, I do not believe there is a simple answer to this question.

First, I would like to discuss how the Human Genome Project differs from standard biological research, a question I am frequently asked. In some ways, the Human Genome Project is different, but in others it is just a natural continuation of biological traditions.

The genome project has a large objective: too large for any single investigator to attempt to achieve in a lifetime. Although the objective is large, it is fairly clear and approachable and lends itself to an organized, collaborative program. Because of the large objective, the Human Genome Project has been called "big science" and accused of being a threat to "little science". In fact, the Human Genome Project is distinguished from other biological projects not so much because it is big, but because it has a clear goal, emphasizes technology development and attempts central coordination. These characteristics have, indeed, caused some purists to reject it as not "science" at all. Biologists have never attempted an organized project of this scope and visibility before

and thus they view it with alarm. How well we succeed will certainly influence the likelihood of any future attempts along these lines.

Although the Human Genome Project is different in having a bigger goal and being more structured and coordinated, it can also be viewed as a natural outgrowth of a long tradition. Geneticists have always been making maps –maps are a natural organizing principle or infrastructure on which genetic knowledge can be built. Maps of simple organisms could be made by a single individual, those of more complex organisms required some dedicated soul who would collect, organize, check, and publish the map as well as resolve discrepancies. This kind of activity was at one time highly valued, though it was never everyone's cup of tea. Today, when there are so many glamorous things that geneticists can do, mapping and assembly of maps is considered somewhat pedestrian by comparison, but the map is still just as important.

The human map is distinguished from previous maps by greater size and comlexity and by the greater detail we are striving for. Until now, someone like Victor McKusick could keep track of all genetic diseases of man and the Human Gene Mapping Workshops kept the whole map up to date on a biannual basis. But the rate of data acquisition and the amount of data is going to increase vastly and manual methods and informal get-togethers will no longer be able to cope. Thus the human mapping enterprise is not different from previous activity but only greater in scope. Therefore, it requires more organization and coordination to flourish.

Why does this create a mandate for more sharing than is traditional in biology?

In standard biological research, the emphasis is on innovative, original ideas and the creation of new knowledge throug cleverness and serendipity. Sharing of results is expected after they are mature enough to publish and free exchange of ideas along the way is lauded, but we do not see any particular virtue to insisting on more. It is generally believed that the autonomy of individual investigators is needed for the best payoff and is indeed essential to creative research.

Although there is room for the idiosyncratic and serendipitous in th Human Genome Project, much of what we are trying to do lends itself very well to teamwork, coordination and sharing of materials and ideas. Indeed, the very ambitious goal that has been set will be difficult to achieve unless scientists work together. Furthermore, without the benefits of mutual reinforcement, it may be difficult to keep up the momentum for 15 years! Sharing will also keep the cost down by avoiding unproductive duplication of effort. Since the Human Genome Project is relatively expensive, it is important to be as economical as possible.

One thing I have become acutely aware of in the past year, is the concern of investigators not involved in the Human Genome Project that all the exciting results will be available to only a select few and that other scientists will be left out. This fear is I think misplaced, because there is no way to hold onto so much information produced in so many different laboratories. However, unless we act to allay the fear, the project may lose support and fail on this account. We must make clear that the purpose of the genome project is to develop fundamental information to be shared with the broader community so that it can be used for innovative research and to develop medical applications. It is incumbent on us to share the results of Human Genome research as rapidly as possible just because they promise to be so valuable to humankind. Information that can benefit all of us must be quickly disseminated.

Since rapid sharing is such a virtue and the arguments for it so compelling, how could there be anything wrong with it? Far be it from me to suggest that there is, but I want to relay some concerns that are being voiced by thoughtful people.

- How can we keep a scientist interested in a line of work, if that scientist does not have the opportunity, at least for a limited time, to analyze the data he or she labored for a long time to obtain?

- In order to preserve the incentive for commercial exploitation of Human Genome Project research, we need to protect intellectual property rights. Rapid sharing can lead to messy trails for claims of ownership, removing the protection needed to provide an incentive for investment. Without investment, much of the benefit of the Human Genome Project may not occur.

Both of these objections are valid and real. We have asserted that we are pursuing the Human Genome Project for the public good, but what is the public good in this context? Is it maximum commercial exploitation? Free and rapid access to all who want the data? The most incentive for those carrying out the work so it gets done? These goals are not all compatible with each other.

I submit it is none of these alone, but a careful balance among them. As a manager faced with setting sharing policies, I need to develop policies that avoid interfering either with progress on the Human Genome Project or with exploitation of the results for the public benefit. Such policies also must be flexible enough to accommodate the needs of different types of research, e.g., mapping information may need different rules from sequencing information or computer algorithms. Currently, at the NIH, we ask each grantee to describe how they will share their results and negotiate with them if the plans do not seem reasonable or are out of line with what others are doing. Eventually, we hope

that the various scientific communities within the genome program will come to a consensus on the appropriate length of time investigators may hold various types of data before releasing them to a database or publishing them.

Any sharing policy we come up with must be fair and equitable and accepted and abided by worldwide. Without agreement on common principles, I cannot see how we can have international cooperation. True collaboration requires agreement on some ground rules. If we do it right, the Human Genome Project could become an example of how planning, cooperation and sharing can be beneficial to the attainment of selected, important scientific goals without being detrimental to the scientific enterprise as a whole.

IDENTIFICATION AND DIAGNOSIS

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ETHICS AND HUMAN GENETICS ONCE THE HUMAN GENOME HAS BEEN MAPPED

John Fletcher

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ABSTRACT

In principle, advances in the scientific-technological field occur so rapidly that it seems difficult to draw up an ethical code or attain ethical consensus among specialists in applied genetics. However, this would pose the following question: is it technology that dictates ethical norms or is it ethics itself that governs the application of science and technology? Logically, an international ethical code should be set up for specialists in genetics that takes into account problems such as free choice in the matter of abortion, confidentiality, respect for privacy or the use of parental diagnosis, amongst others.

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Thank you, Dr. Scriver. My sincere thanks to the organizers of this meeting for the invitation to come here. The title of my talk is "Ethics and Human Genetics After the Human Genome is Mapped." After a brief description of the most prevalent ethical problems in applied human genetics, I conclude with a proposal of some rudimentary elements of an international code of ethics for human genticists.

Applied human genetics has four service activities: genetic screening (of carriers and newborns), counseling, prenatal diagnosis, and treatment or medical management of genetic disorders. Any analysis of ethical problems in this field and any proposed code of ethics must presuppose and encompass these activities.

Any consideration of ethical issues in human genetics must begin with the unique position of human geneticists today. Human –or medical– geneticists are unquely situated at the first major subspeciality to interact with individuals and families about genetic problems and decisions to be made about genetic problems and decisions to be made about them. Medical geneticists are the mediators of genetic knowledge, gleaned from mapping and sequencing, to patients, families, and whole populations. They also have the most collective experience in responding to these problems. Any study of these problems would wisely begin with them –and their parents– to understand the dynamics and outcomes.

The unique position of human geneticists in science and society leads to my major thesis, namely, that this group of professionals in many nations have a special responsibility to take the lead to work out approaches to the ethical problems that they share with their patients. Who can do this task better than the geneticists, in reflection with patients, their families, and others interested in study of ethical problems?

Four premises underlie my comments, based on social scanning of the future, which is a risky business. The first premise is that the Human Genome Project will succeed technically. Whether the timetable will be shorter (as Dr. Gilbert believes) or longer (as I believe, given human nature, rebellions within science, political problems, etc.) is immaterial to the premise. Another source of delaying clinical benefits of the Human Genome Project, in the United States, in moratoria, bans, and lack of support in federal science for applied genetic research [1].

Secondly, genetic services (the four activities listed above) will gradually become part of the national health plans of all developed and developing nations. Third, genetic knowledge will gradually become a normal part of everyday life, because genetic information will transform the practice of medicine. Professor Jonsen has described this transformation eloquently today. Child-

ren will be raised with the intuition that it is good to want to know about themselves genetically to prevent harms to themselves, their children, and to future generations. The fourth premise is that a set of ethical agreements about the use of genetic knowledge in medicine and society is already present in the practices of human geneticists in many nations.

Everyone who has studied ethical problems in human genetics agrees that the problems that occur now and the problems when the genome is mapped will not be significantly different in kind, but they will be different in magnitude. The ethical problems of the "old and new" genetics are not different in type but in scope and the vast numbers of individuals and families affected. An international study in 19 nations [2] has shown that human geneticists and their patients in many nations frequently face a set of eight ethical problems, also illustrated in the following table.

Table 1. Ethical Problems in Human Genetics

1. Fairness of access to genetic services.
2. Abortion choices.
3. Confidentially problems when other family members' interests are involved.
4. Protection of privacy from institutional third parties: insurers, employers, etc.
5. Disclousre dilemmas in counseling.
6. Indications for prenatal diagnosis: sex selection, benefit to third parties.
7. Voluntary or mandatory screening policies.
8. Counseling incapacitated patients: directive vs. non-directive approaches.

I rank the problem -in terms of frequency and importance- in this order based on information from geneticists obtained in an international study, frequency of discussion in the literature, and in terms of numbers of persons who might be adversely affected by the problem itself. These problems have been thoroughly described elsewhere [3].

My thesis is, that since a strong to moderate consensus exists among medical geneticists' approaches to these problems in many nation, they have a special responsibility to take the lead to lay the foundations, in this generation, for the approaches that they and their successors will take in the future when the genome is mapped. Now is the time for clarification and shaping approaches to ethical problems that will serve well into the future.

Is an international code of ethics and practise among geneticists really possible –or even needed? The need arises from the problems, listed above, which are significant. There are arguments against the concept and utility of a code of ethics, which are: 1) "ethics" is too subjective and culturally variable to establish a consensus, 2) technology changes too fast to establish ethical

consensus, 3) risk of legal liability if geneticists act in a way to deviate from the code's specified practices, and 4) other subspecialties in medicine do not have codes of ethics.

Each of these arguments can be, in my view, successfully met and rebutted. First, evidence from the study cited above shows that medical geneticists across several cultures not only identify a highly similar set of problems but share similar approaches to many of them. They do not necessarily agree on *specific resolutions* of some ethical problems (especially conflicts of confidentiality between the patient and family members, disclosure of psychologically sensitive information, and indications for prenatal diagnosis) but they do share similar values in how these problems ought to be considered and evaluated. As long as a code of ethics did not attempt to dictate outcomes for particular cases and acknowledged widely accepted exceptions to moral principles, a code for medical geneticists, like international codes for research involving human subjects [4], would be acceptable and useful.

Secondly, although technology does change and evolve, technology itself ought not to dictate what ethical standards should be employed for its proper use. Unless this is true, "ethics" is a sham anyway. Thirdly, if geneticists act contrary to a code's general expectations, they should have ethically defensible reasons that would likely be covered by the exceptions recognized by the code. Also, to cite legal risks begs the question of whether the actions of such geneticists would be ethically acceptable in the first place. Fourthly, even if other subspecialities did not (which is not true) have bodies of ethical reflection and guidance, it would still be a weak argument. Other subspecialities are not in the unique position of geneticists, namely, that they mediate knowledge to patients about their destinies and wellbeing. Other subspecialities have, in fact, surveyed their members about ethical problems, analysed the data, and shaped guidelines for their members on some problems [5].

Arguments for a code of ethics are: 1) geneticists in this generation need to consolidate their moral experience, which is considerable, to transmit to the next generation, 2) achieving consensus on less complex ethical issues can be a floor from which genetiscists can consider more complex issues to come, when the genome is mapped, 3) geneticists have an important opportunity to influence evolving public policy with a code of ethics, and 4) since medical geneticists in many nations would like to develop a specialty in this field, a code of ethics is a mark of a profession and speciality.

The rudimentary elements of an international code of ethics for human geneticists would include a preamble describing the issues, problems, values, principles, and relationships that geneticists and their patients, families, and societies face in this field of

endeavor. There could follow sections that address the eight problem areas described above. Based on the knowledge that we have about medical geneticists' approaches to these problems, the following sections are proposed.

1. Access to Genetic Services

Securing access to adequate genetic services is an ethical obligation of society to persons and families as part of a general obligation to secure access to adequate health care. Equitable distribution of genetic services is owed first to those whose need is greatest, those at higher genetic risk. Geneticists should do everything within their legitimate authoroity to insure that patients who most need services and have the greatest opportunity to benefit receive such services.

2. Respect for and Safeguarding Parental Choices

Geneticists in all nations consider it essential to protect rights of parental choice. Medical geneticists should safeguard the options of parents in genetic services, including the options of abortion or to carry to term a fetus with a malformation or a genetic disorder.

An exception to this duty should be made in decisions that involve information about the gender of the fetus, unrelated to genetic diseases, that may lead to abortion. Geneticists have no duty to cooperate with parental desires to abort for gender selection, because 1) gender is not a genetic disease, 2) equality between males and females is vilated, and 3) sex selection is a precedent for eugenics (i.e., interventions in human reproduction with regard to characteristics unrelated to a genetic disease). Sex selection discredits the role of prenatal diagnosis in medicine.

3. Confidentiality When Other Family Members are at High Risk

Confidentiality is a vital but not absolute norm in medicine and in medical genetics. If the patient refused to disclose proven risks of harms to relatives, the imperative of prevention of harm to others limits a physician's or counselor's duty of confidentiality. The President's Commission for the Study of Ethical Problems in

Medicine recommends that confidentiality be breached only in exceptional circumstances that meet four conditions [6].

Legal protections for geneticists who breach confidentiality to warn others at high risk, after having complied with these conditions, may be necessary in the future.

4. Protection of Patients' Privacy from Institutional Third Parties

Without effective legal protection from genetic discrimination in employment, employers should not have access to personal genetic data. Even when legal protections have been adopted, access to personal genetic data should only occur with the informed consent of the individual involved. In nations where private health insurance is a major industry and third party payer for health care, the industry should be regulated by government to discourage excessively costly premiums for those at known higher genetic risk. Refusal of private health insurance to families at higher risk for genetic disease should be illegal. Another alternative is government underwriting of health insurance for those at genetic risk.

5. Full Disclosure of all Clinically Relevant Information

Medical geneticists should disclose all clinically relevant information to patients and family members, consistent with considerations of immaturity and psychological well-being. Also, the capacity of counselees to comprehend information and make voluntary choices are morally relevant factors in disclosure dilemmas. Psychological assessments of capacity are best done in consultation with mental health professionals. Psychologically sensitive information, such as XY genotype in a female, should be disclosed only the context of full on supportive counseling and patient education.

6. Indications for Prenatal Diagnosis

Prenatal diagnosis should be used only to give parents and physicians information about the health of the fetus. Any other use, such as for sex selection (except for X-linked disease) or for tis-

sue typing to plan for transplantation to benefit another person after birth, should be avoided. If patients have a genetic reason for diagnosis and also show excessive interest in the gender of the fetus, geneticists can consider delayed disclosure of gender after timely disclosure of clinical findings.

Laws prohibiting abortion for sex selection are appropriate only wher there is evidence that abuse of the medical indications for prenatal diagnosis exists. Where abuse does not exist, laws prohibiting sex selection abortions are not only unneeded but set harmful precedents restricting abortion choices.

7. Voluntary Approach to Genetics Services: One Exception

Genetic services programs should be voluntary in nature, with one exception, i.e., screening newborns when treatment is available to help those affected by genetic disorders. Forcing persons to submit to genetic services to prevent genetic disorders violates the principle of respect for persons and disrupts their relationships in families. Coercion, arbitrariness, and discrimination against persons at higher genetic risk should be illegal in the context of employment and educational opportunities.

8. Non-directive Counseling: with One Exception that Requires Further Study

Non-directive counseling, i.e., to refrain from direct moral advice to protect and enhance the autonomous choices of patients, is a commitment of medical geneticists,assuming that all relevant facts are known to the counselee to consider the facts in the context of his or her beliefs and values.

A possible exception to non-directive counseling can arise in genetic counseling with incapacited patients, especially when genetic harm to others is a clear and present danger. The actual incidence of this type of situation and geneticists' response to it needs careful study, in principle, giving direct moral advice to relatives of incapacitiated counselees or to impaired counselees themselves is ethically acceptable, if the likelihood of harm to others is great and in the geneticist has informed the patient and/or relatives in advance of counseling that "directive counseling" may be indicated. Geneticists should follow established protocols in determining the capacity of their patients.

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6. **Presidential Commission, 1983:** *Screening and Counseling for Genetic Conditions* (Washington, D.C., U.S Government Printing Office, p. 44. These conditions are as follows: 1) that all reasonable effort to obtain voluntary consent to reveal the situation have failed; 2) that there is a high probability both that serious harm will be entailed is information is concealed, and that the information revealed will be used to avoid such harm; 3) that certain identifiable individuals could suffer serious harm and 4) that adequate precaution has been taken to guarantee that the necessary genetic information will only be revealed for the diagnosis and/or treatment of the disease in question.

DIAGNOSTIC TESTING OF GENETIC DISORDERS IN THE EARLY STAGES OF PREGNANCY: SOCIAL AND ETHICAL IMPLICATIONS

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ABSTRACT

There are currently two options for the prevention of genetic disorders: the donation of gametes together with assisted reproduction and pre-natal genetic diagnosis followed by selective abortion of an affected fetus. Diagnosis can also be carried out prior to the implantation of the egg (post-conceptional diagnosis), and it has recently been suggested that the biopsy of the polar corpuscule will facilitate prediction of the genetic constitution of the ovum to be fertilized.

On the ethical aspects of pre-natal diagnosis, the author thinks that use for eugenesic ends is unacceptable and that the fundamental aim of this diagnosis is to accurately inform parents and offer them all options that could fit their case, thus making it possible for them to come to a decision.

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During the last two decades there has been an increasing interest in congenital disorders and human genetics. Congenital disorders have not only become the major cause of infant mortality, but are also responsible for a considerable proportion of long term physical and/or mental handicaps. Moreover, a growing number of couples want to limit their family size and protect the quality of life, and they are less inclined to consider the birth of a handicapped child as an unavoidable risk. Therefore, they want to be informed about the genetic risks and how to avoid having an affected child.

To face reproduction and prevent genetic disorders associated with poor quality of life two options are mainly available (tab. 1): gamete donation together with assisted pregnancy procedures, or prenatal genetic diagnosis followed by selective abortion of an affected conceptus. In the recent years we have witnessed the growth of a number of prenatal diagnosis methods from applied research to being a routine component of genetic couselling and obstetric management. About two hundred genetic conditions can actually be diagnosed in utero by applying invasive sampling techniques (chorionic villus sampling, amniocentesis, cordocentesis), and cytogenetic, enzymatic and DNA analysis methods. In addition, more than two hundred structural defects of the embryo/fetus are detectable by sonography, and neural tube defects, and Down syndrome can be screened on maternal blood in the early second trimester of pregnancy (tab. 2).

Table 1: Reproductive options available to genetic risk individuals for avoiding an affected child

BEFORE CONCEPTION:

- In the case of autosomal recessive disease: do not reproduce with a carrier of the same abnormal genetic trait (i.e.: contraception, sterilization).
- In the case of X-linked or autosomal dominant disease: do not reproduce at all.
- Ovulation induction, first polar body biopsy and genetic analysis, together with IVF-ET.

AFTER CONCEPTION:

- Unselective abortion.
- Preimplantation genetic diagnosis and transfer of only non affected embryos.
- Post-implantation genetic diagnosis followed by selective abortion of affected embryo/fetus.

IN THE FUTURE:

- Fetal therapy (stemm cell transplantation, gene therapy).

In all three invasive sampling procedures, when correctly applied, maternal and fetal risk has proved unusual, while in skilled hands the sampling success rate is virtually a hundred per cent and abor-

tion rate is about one per cent (tab. 3). However, surgical or medical selective abortion after amniocentesis or cordocentesis can not be performed before the fifth month, of pregnancy and implies not only significant maternal mortality and morbidity but is also a psychologically traumatic event with frequent long term behavioural and emotional sequelae. In fact maternal-fetal bonding has already occurred at the fifth gestation month and prenatal attachment to a wanted child exists. Fortunately, chorionic villus sampling (CVS) allows prenatal diagnosis to be made much earlier in pregnancy: at that time gestation is still a private event and no human features can be recognized in the sonographic representation of the embryo. The psychological advantages, compared to amniocentesis and cordocentesis, seem obvious.

Table 2: Currently available methods for in utero diagnosing congenital abnormalities

ULTRASOUND*:		>200 abnormalities have already been identified
CVS	Biochemical analysis	> 100 metabolic diseases
AMNIOCENTESIS	Cytogenetic analysis	Chromosome Aberrations
FBS	DNA analysis	> 50 monogenic diseases
MATERNAL BIOCHEMISTRY**:		– NTDs Screening – Aneuploidies Screening

* mainly in the 2nd and 3rd trimester.
** at 15 to 18 gestation weeks.

Table 3: Characteristics of the invasive prenatal diagnosis methods

Method	Earliest week for sampling	Time to diagnose	Abortion risk	Maternal risk	Fetal risk
CVS	6	1 day to 2-3 wks	1 %	excep-tional	excep-tional
Amniocentesis	15	2-4 wks	1 %	"	"
FBS	17	1-3 days	1-4 %	"	"

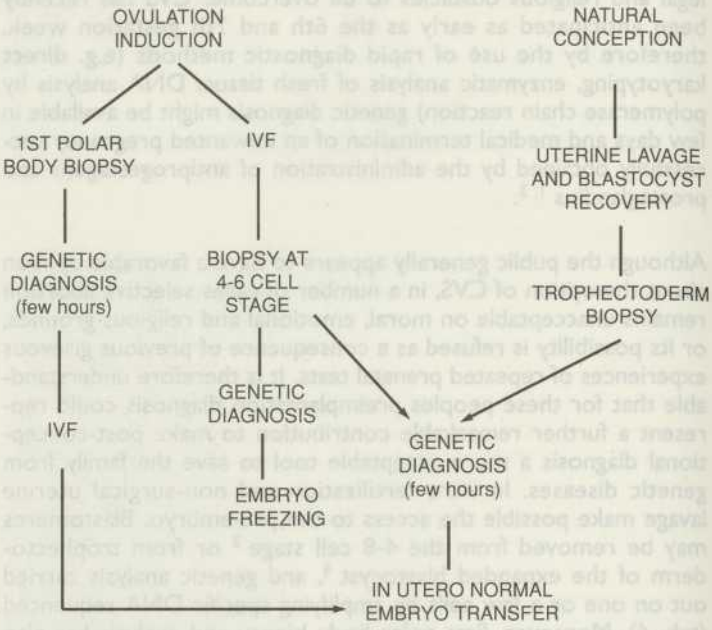
First trimester genetic diagnosis by CVS has become a widely accepted alternative to the second trimester procedures. CVS has offered the opportunity to greatly relieve the anxiety caused by the long wait of a diagnosis concluded next to the fifth month of pregnancy, and to minimize the obstetrical and psychological

complications of a late selective abortion. Moreover, because of its precocity first trimester diagnosis has frequently allowed even legal and religious obstacles to be overcome. CVS has recently been anticipated as early as the 6th and 7th gestation week, therefore by the use of rapid diagnostic methods (e.g. direct karyotyping, enzymatic analysis of fresh tissue, DNA analysis by polymerase chain reaction) genetic diagnosis might be available in few days and medical termination of an unwanted pregnancy successfully obtained by the administration of antiprogestagens and prostaglandins [1, 2].

Although the public generally appears to have a favorable opinion about the option of CVS, in a number of cases selective abortion remains unacceptable on moral, emotional and religious grounds, or its possibility is refused as a consequence of previous grievous experiences of repeated prenatal tests. It is therefore understandable that for these peoples preimplantation diagnosis could represent a further remarkable contribution to make post-conceptional diagnosis a more acceptable tool to save the family from genetic diseases. In vitro fertilization and non-surgical uterine lavage make possible the access to the pre-embryo. Blastomeres may be removed from the 4-8 cell stage [3] or from trophectoderm of the expanded blastocyst [4], and genetic analysis carried out on one or a few cells by amplifying specific DNA sequenced (tab. 4). Moreover, first polar body biopsy and analysis has also been recently suggested and successfully applied to predict the genetic constitution of the oocyte to be fertilized [5]. However, diagnostic reliability and conceptual risks of gametes and preembryo manipulation have been evaluated only in animals: by extrapolatin the results to humans, teratogenic effects might be excluded, while a lower implantation rate and reduced growth potential should be expected [6]. At present preimplantation and preconceptional diagnostic procedures can only be offered to highly motivated and fully informed couples at risk of hereditary disease.

The actual maternal age criteria, limiting the offer of genetic diagnosis to women 35 or more years old, has little impact on the incidence of chromosome anomalies at birth: since up to 90% of birth are in fact from lower age class women as well as 70% of Down S. newborns. On the other side the limited laboratory facilities, which are unlikely to be significantly increased in the future, make it unrealistic to extend prenatal tests to all pregnant women. Therefore, the avaliability of inexpensive and simple screening tests could have a beneficial effect to identify higher risk pregnancies without considering maternal age. Accumulating evidence support the association between abnormal maternal serum values of alfa-fetoprotein (AFP), human chorionic gonadotrophin (HCG), and unconjugated oestriol (uE3) in the early second trimester and viable fetal trisomies. The data early second trimester and viable fetal trisomies. The data show that by offering amniocentesis to only 5% of the total pregnant population,

Table 4: Methods that are being considered for preimplantation genetic diagnosis



over 60% of Down S, would be detected [7]. However, the prevention of aneuploidies by second trimester programme and late termination is a very distressing task, and the development of an equally efficient screening in the first trimester would be highly desirable. Preliminary studies suggest the high sensitity of fetal/placental proteins (AFP, PAPP-A, SP-1) between 8 and 10 gestation weeks: in 85% of fetal aneuploidy cases the maternal level has been reported below the 5th percentile of the normal distribution in at least one of the markers [8]. Further improvements in sensitivity are expected by using information derived from assay of other pregnancy markers (e.g. CA 125, uE3) in maternal serum. Thus, measuring first trimester concentration of maternal serum gestational proteins is likely candidate to becoming an effective means of identifying pregnant women in the general population who are at increased risk of bearing a fetus with chromosomal aberration and to whom chorionic tissue karyotyping should be offered.

In addition, the new methods for human DNA analysis promise radical advances in the prevention of inherited disorders. The chromosomal location of defective genes, that cause about 600 single-gene disorders, have now been identified and many of them, including the most important ones, may be detected during pregnancy. A widening range of detectable diseases is becoming accessible and molecular studies by DNA recombinant technol-

ogy will provide in the next twenty years a complete linkage map of the Human Genome. Therefore, disorders with life threatening, moderate or hardly noticable symptoms, or which manifest later in life (e.g. Huntington's disease, policystic kidney), genetic predisposition for certain diseases (e.g. diabetes, cardiovascular diseases), and even cosmetic characteristics could be recognizable prenatally in the future. On the other hand, the methodological advances in prenatal diagnosis are undoubtedly speeding the evolution of new areas of in utero medical intervention, namely somatic/germinal gene therapy and stem cell transplantation, to cure genetic diseases and ensure the quality of life.

In this context a number of implications are controversial enough and need to be fully debated both professionally and among the wider public. They arise from, among other things, the fact that early CVS, preimplantation embryo biopsy, sorting of fetal cells in maternal blood, selection fo spermatozoa, etc., will make genetic diagnosis a more acceptable tool for a wider number of people to select whether the conceptus be born. Moreover, genetic manipulation of the pre-embryo is potentially a very positive development that help to correct numerous devastating genetic disorders in time. It could also have the potential harmful effect of engineering humans in the laboratory according the formulae of supermen or bizarre monsters.

Should prenatal testing be provided for all women wishing to have a "normal" baby or restricted to higher genetic risk couples?

Should a pregnant woman do what she can to ensure the birth of a normal rather than a handicaped child?

Does it make sense to establish criteria to discriminate between minor and major disorders with regard to the admission to prenatal testing and/or selective abortion?

With the new development of fetal and gene therapy the conceptus has the potential to become a patient who might not only be diagnosed, but also treated. Fetal treatment brings the maternal-fetal conflict issue into sharp focus: can fetal abnormality be corrected; to what extent; and at what maternal and fetal risk? Is germ cell gene therapy acceptable in human beings?

To help the general debate on ethical issues raised by genetic diagnosis in early pregnancy each participant should be scientifically informed, firmly committed to indiviudal rights and human dignity and should openly accept a free society of pluralistic values.

The use of prenatal diagnosis for a directed eugenic programme at the population level is unacceptable. Access to prenatal testing should in principle be made available to all individuals. The only limiting factor might be represented by the availability

of financial resources in the context of the health policy of the society (selective criteria should be determined by the community).

The objectives of prenatal diagnosis are to allow the wides possible range of informed choice regarding the prospect of having a genetically defective child. For the vast majority of conditions that can be diagnosed in utero no cures or treatments are known, therefore selective abortion is the decision to interrupt pregnancy is part of a woman's right to an abortion is always absolute, the dispute about major and minor defects and the attempt to establish general criteria according to what a conceptus should be aborted become irrelevant. On the other side, any ethical justification to selective abortion should be fundamentally found in the complexity of facts and motivations peculiar to each individual.

The effects of induced abortion as a result of prenatal diagnosis are frequently reported as psychologically traumatic: for most women the event involves the loss of a desired child to which they directly contributed by their active decision to abort. There is no doubts that the access to the new fetal therapy approaches, namely stem cell transplantation and somatic gene therapy, would provide the great advantage of avoiding the moral pain of selective abortion. However, in no way should fetal therapy be undertaken forcibly or when causing harm to the mother.

Table 5: Future directions to prevent, diagnose, and cure the genetic disease

- Carrier detection of abnormal genetic trait.
- Maternal serum biochemical screening of embryo aneuploidies in the first trimester.
- Magnetic nuclear resonance of the fetus.
- Genetic diagnosis on fetal cells in maternal circulation.
- Separation of X- and Y- bearing spermatozoa.
- Medical therapy (drugs administration in fetal circulation).
- Surgical therapy (open uterus surgery).
- Stem cell transplantation.
- Somatic cell gene therapy.
- Germ cell line therapy.

Germline genetic engineering is not yet with us, nevertheless there are real causes form concern about it. The eventual mapping and sequencing of the Human Genome, together with knowledge of how genes determine diseases and affect characteristics, may one day make genetic manipulation of the human embryo possible. It has been claimed that the wrong decisions in the application of this research could have disastrous consequences on the human species and society. This concern is not substantially

different from that resulting from other research areas (e.g. nuclear energy). Then, is this fear a valid motivation to ban any genetic research on embryos? As a general rule to face these problems correctly "any constructive dialogue and reasonable policy development should be pursued by putting research oversight into a multidisciplinary review body suitably constituted to evaluate not only technical risks, but political, social and moral aspect as well" [9, 10].

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PROFESSIONAL SECRECY AND CONFIDENTIALITY

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CONFIDENTIALITY

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ABSTRACT

The European Community is currently financing a programme of research and development for the study of the Human Genome. This project is of a certain confidential nature. The EEC guarantees confidential treatment of technical reports to avoid the commercialization of certain information. Besides, intellectual copyright belongs to the researchers and it must be them who exploit the information, bearing in mind that there will be no exclusive exploitation right as far as the human ADN is concerned. On the other hand, the Commission also guarantees the anonymity of personal data resulting from genome research, considerin that the people whose ADN's are being mapped have given their consent to this end after being informed of the project. Finally, the medical data must only be used for diagnosis and the prevention of diseases or for research. Therefore, access to this information must be controlled.

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Thank you, Mr. president. When just a few days ago, Doctor Grisolía requested me by telefax to provide a presentation on confidentiality for this workshop, I accepted immediately because it provides me now with an opportunity to discuss in public some reflections on a matter perhaps small –in quantitative terms of our budget; about 1% of our 1990 European Communities budget for R&D– but you will agree with me that it is very important in quality: the legal problems of Human Genome research.

My job in the last couple of years has been as legal adviser for the Science and Research General Directorate of the European Community in Brussels. Of course, I speak here on a personal basis –that will make things easier. As you already know, the EC has also adopted this year a small, pilot R&D programme for Human Genome analysis. As Doctor Loder and Proffesor Niermeijer are present in this workshop, and they are far more competent to give you any information about the scientific and technical contents of our programme, and we have a couple of information packages for those who are interested, I will concentrate here on the institutional concerns raised, mainly by the European Parliament, during the legislative process which has eventually made the Commission –that is, the administrative executive body of the European Communities– responsible for a thorough debate of the ethical, social and legal problems of Human Genome analysis. As Prof. Niermeijer told you this morning, there will be a general ethical review of the programme by an independent interdisciplinary committee of thirty members, to be nominated at the beginning of next year... which, by the way, will also include patients' representatives, of organizations of relatives of patients, like cystic fibrosis. We think that this is also an important aspect for an ethics committee.

Confidentiality for R&D

The Commission must also ensure –that was a commitment to the European Parliament– specifically the exclusion of any alteration of human germ cells during the research. This has been criticized here, perhaps rightly, but it is a legal obligation for us. And the Council decision requires full confidentiality of any personal information collected in the course of the research, which will conform to the best data protection practices. I will consider here *four aspects of confidentiality for the Human Genome Programme*; the three first concerns the research itself. First, *contractual* confidentiality, second *medical* confidentiality, and third *data protection*. And the fourth, the issues raised by *applications* of any new knowledge arising from the research.

First, we begin with *contractual confidentiality*. On the one hand, there are administrative procedures: all proposals and all technical reports, are treated confidentially by the Commission's services, by the Advisory Committee and by their experts. However, some reports suitable for publication, excluding any commercially sensitive information, must be provided. No publication of results will be made without the prior agreement of the contractor. On completion of the project, a confidential report must be submitted to the Commission, indicating how the contractor intends to exploit the results of the work, including the industrial and intellectual property rights applied for and received. The Commission may submit the full technical report, on a confidential basis, to other EC institutions, like the European Parliament, and in agreement with the partners, to governments of the EC member states on international organizations.

On the other hand, the contractual obligations include a limitation of ownership. We have in the Commission the general principle that ideas and intellectual property rights generated under the research contract are owned by the contractors, who must exploit or commercialize them in conformity with the interests of the Community represented by the Commission. The contractual conditions provide a legal framework for the granting of licenses and use rights between different projects and different RTD (Research and Technological Development) programmes. Information which cannot be protected by patents –that would be the case in Europe, of human DNA sequencing– must be made available to other entities, subject to agreed qualifications and restrictions... this is perhaps a bit too technical, but it is carefully regulated in our harmonized or "model contracts". In the case of human genome analysis, there is an additional principle, specific to this programme, namely that there shall be no exclusive exploitation rights in respect of human DNA. But fortunately –I hope, because Mr. Triana's availability is not confirmed– I will leave this difficult subject of intellectual property rights to the last speaker of the panel, or otherwise we can discuss it in the colloquium.

Medical confidentiality

The second aspect I want to consider here is *medical confidentiality*. The Commission fully respects the Council of Europe recommendation of February 6, 1990, which shall be included in a future European convention concerning medical research on human beings. It is being drafted now by experts for the Council of Europe. I think Mr. Wit, who is here, is working on that also. Principle 3 of this recommendation states that "no medical research may be carried out without the informed, free, express and spe-

cific consent of the person undergoing it". And Principle 9 declares: "Any information of a personal nature obtained during medical research should be treated as confidential". The members of the 60 "large families", whose DNA is collected and mapped through the European Human Genome Programme, have been fully informed, and all of them have given their free and written consent, after a long interview in which clear and pertinent explanations were given, not only about the commitment, but above all about the possible risks involved. The Commission therefore guarantees the confidentiality and anonymity of the personal data to be obtained; for example the DNA samples to be distributed to laboratories engaged in the linkage mapping are coded, and the key to the code is not stored on computer.

Informatic confidentiality

We comes now to the third aspect of confidentiality, namely *data protection*. This is perhaps one of the most conflictive ones –even the most conflictive one– because different and fundamental rights are at stake. The right to privacy is certainly one of the essential human rights, but yet it is not an absolute one, and there is a constitutional case-law in several European states, particularly in the Federal Republic of Germany, setting up limits on the right to confidentiality for personal data. Indeed, the European Convention on Human Rights considers the protection of health as a legitimate limit to the right to privacy, which itself is also a limit to the freedom of expression. You will find that in article 10 paragraph 2 of the Convention. A comparative survey of national and international legislation on privacy of data protection shows that a set of principles has emerged to reconcile two seemingly conficting needs: on the one hand, freedom to receive information through the new computer and telecommunications means –we could in fact speak of telematies, the mixture between telecommunications and informatics; and, on the other hand, respect for the private lives of individuals. These principles include: 1) Fair and lawful collection of data; 2) Quality of data, including accuracy and pertinence; 3) The principle limiting the use of data so that dissemination and interconnection are made conditional upon the consent of the persons concerned, or the existence of a specific legislative authorization; 4) Transparency, whereby information about the existence of data banks, their purpose and use, are to be made public; 5) The principle of individual participation, by virtue of which the individuals concerned should have access to files, and even a right to have such data corrected or erased, although in some countries there are limits for correction of medical data by the individual; and finally, the principle of responsibility of those in charges of files.

These are differences between the laws. Some are general; in other nations they only cover specific areas –this is mainly the

US approach. Great importance therefore, at least in the European setting accrues to the Council of Europe Convention on the protection of individuals with regard to the automatic processing of personal data –this is the official title– of 1981, which the Commission fully intends to respect, and which can be safely taken as a model set of international standards in this area.

Therefore, international access to human sequencing should include full respect for data protection, and of course of international standardization in this area, and guarantees against undue access to private data.

Of course, automatic medical data banks should only be stored for the purposes of medical care, diagnosis and prevention of disease, *and* scientific research in this area. Access to map and sequence information in data banks and clone repositories must be open to scientists and therefore subject to unavoidable controls. However, *long-term* storage of such data requires specific and increased security –alphanumeric passwords, electronic signatures, etc. As the data for the Human Genome Programme may concern several generations eventually, and in addition certain genetic disorders (Huntington's chorea for example, which may only appear at later stages in this life of a patient, between 35 and 55), long-term conservation of data is justified on a number of grounds.

Consideration should be given to the need to ensure that backup records are kept at a safe, remote site. It goes without saying that personnel who are authorised to access the date should be trained to respect and implement data security.

The right to confidentiality of personal genetic information is potentially conflictive with the rights of others: family members, fellow-employees, the public at large. For example an individual may have DNA data such as knowledge of a gene mutation causing, say Huntington's disease again, which another member of the family needs for diagnosis or prevention. There are also risks for the individual himself. Information which is relevant to her or his well-being must be available when needed. Knowledge of sensitivity to a particular anaesthetic can save a patient's life as long as it is there when the occasion demands. An absolute ban on disclosure of genetic information would be unworkable, and it would not be in the interests of the individual himself. As was said yesterday, one should not make absolute what is only relative. We don't need absolute but only relative restrictions. I quite agree with that. Privacy should be a vital principle of medical genetics, but departures –for instance information which may be available to family members– must be clearly regulated.

We reach here *the limits of future applications*, the last point. It is essential to ensure that information about their genetic make up or identity, is not forced on individuals, while guaranteeing them the right to know whether they are at genetic risk, so that they can modify that risk, e.g. by a change in life-style. For the future, confidentiality of the data obtained and protection against unauthorised access by third parties, will become crucial.

We are conscious, as the American experience –which has been clearly shown in this workshop– already indicates, that one of the main risks of future genetic testing for susceptibility to disease in the misinterpretation of test results by individuals, families and social institutions, and the potential for stigmatisation and discrimination. These risks will broaden as gene-based test for multifactorial health problems are developed.

But, beyond improving understanding, the main way to prevent unfair use of genetic information is to legally protect its confidentiality; and several fields must be considered; genetic testing for insurance and for employment are the subject of further communications today and I will not go into it; reproductive choices have already been dealt with; the right of parents to full information, in complete confidentiality and freedom from coercion; –at least the ideal; the legal issues are always ideal and often not very realistic–; and, given the wider availability to prenatal diagnosis, the danger that resources for the genetically handicapped may be limited. All these future and not-so-future issues, some of which have already been dealt with today, emphasise the principle of confidentiality. The legal consequences of the principle that personal genetic information must remain confidential, should be the right for everyone not to be discriminated against, on the grounds of one's genetic constitution. Effective protection and access to justice against; genetic discrimination are necessary and fair.

Some conclusions

I would like to add *two concluding remarks*: One, We must consider all these issues from the full respect of the *fundamental principle of scientific freedom*, freedom in many countries, including Spain, by own, is also a constitutionally guaranteed freedom. Only freedom can entail responsibilities. And we care about confidentiality precisely because we care about responsible freedom. It is probably true that human dignity would not be possible without the freedom of science.

My last remark: Human Genome analysis is a *worldwide* research effort, lending itself particularly to cooperative action. It was said

this morning that *sharing data is an ethical imperative*, and I agree. The free exchange of data and materials is extremely crucial in this enterprise. The resources required are so large that unnecessary duplication or undue competition must be avoided. Therefore, the right combination, the right balance of *open collaboration* in scientific research for the benefit of mankind, with full *respect for anonymity of personal data*, must be ensured. Thank you.

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GENETIC TECHNOLOGY, INSURANCE AND THE FUTURE

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ABSTRACT

The insurance industry, as far as life, invalidity and sickness insurance are concerned, is affected by health, the specifying of the premius for the different types of insurance requires statistic analysis of the whole of population data. The assurer moreover examines the health of the candidates and on the strength of both statistic and individual information, sets a reasonable, fair premium. On the other hand, insurance companies consider genetic information to be of interest as far as pre-natal diagnosis and genetic manipulation are concerned. The assurer already has certain genetic information for medical questionnaires include questions or diseases suffered by parents.

The assurer asks whether people who have certain genetic information would adjust their life-style according to same. In fact, it is probable that genetic research will pave the way to a better future, at least as far as health is concerned.

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The insurance industry, as far as life, invalidity and sickness insurance are concerned, is affected by health, the specifying of the premia for the different types of insurance requires statistic analysis of the whole of population data. The assurer moreover examines the health of the candidates and on the strength of both statistic and individual information, sets a reasonable, fair premium. On the other hand, insurance companies consider genetic information to be of interest as far as pre-natal diagnosis and genetic manipulation are concerned. The assurer already has certain genetic information for medical questionnaires include questions or diseases suffered by parents.

The assurer asks whether people who have certain genetic information would adjust their life-style according to some. In fact, it is probable that genetic research will pave the way to a better future, at least as far as health is concerned.

The insurance industry has known a relatively calm period as far as health related insurance policies are concerned. The importance of health is involved in the following categories of insurance: life insurance (including pensions), disability insurance and health insurance. Of course certain problems have arisen: the ever decreasing mortality rates and the coinciding increase in the average age of the population, the increasing number of those unfit to work (with a characteristic sensitivity to economic fluctuations), rising absenteism with definite economic consequences; furthermore we can see a rise in health insurance premiums, not because the number of hospitalizations has risen, but because of the wide range of opportunities that medical technology has made available; furthermore the increase in average age has influenced demand.

If we examine the underlying risk factors of these forms of insurance (mortality rate, sickness rate, etc.) we become aware that nothing has changed in the way we apply these foundations. How and where do we get the necessary information?

In order to determine the premiums for the various types of insurance, one has to gather statistical material. Of course we are only able to do so for periods in the past; one of the fundamental problems is to predict the future development of these data.

Data are accumulated either by observing the entire population (as is often the case in life insurance: the mortality table) or by using the material of (joint) insurance companies (often done for other types of insurance).

The outcome is no more than a mere average. If we confine ourselves for a moment to life insurance: the mortality risk for a 40-year old is 0.00174.

This is derived by dividing the number of 40-year olds that died (d40). It is a deterministic frequency in the meaning as defined by Laplace. We can do this for each age, thus forming a mortality table. The mortality table enables us to calculate what the average life expectancy of a forty-year old is. We find this to be 35.8 years, which follows from

$$e_x^0 = 1/2 + (l_{41} + l_{42} + \ldots\ldots + l_w)/l_{40}$$

This quantity is also an entirely deterministic one.

Obviously not every 40-year old will have this life expectancy. Some will have a shorter life expectancy and others a longer

one. On the basis of the constructed mortality table we can compute how many forty-year olds have a life expectancy of one year, of two years and so on. This results in the following picture:

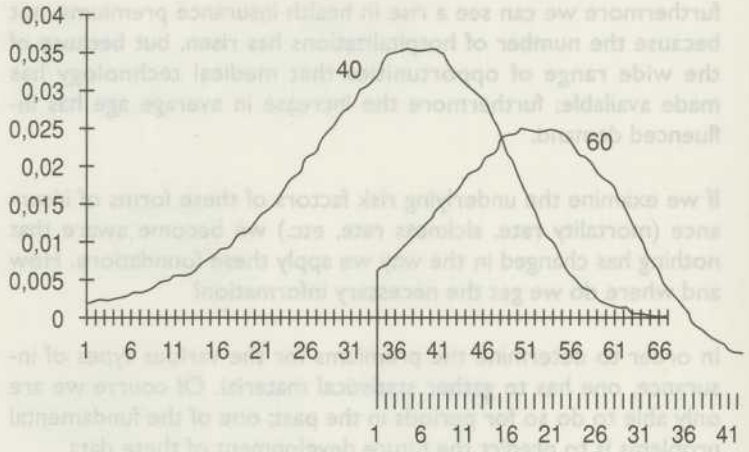


Illustration 1

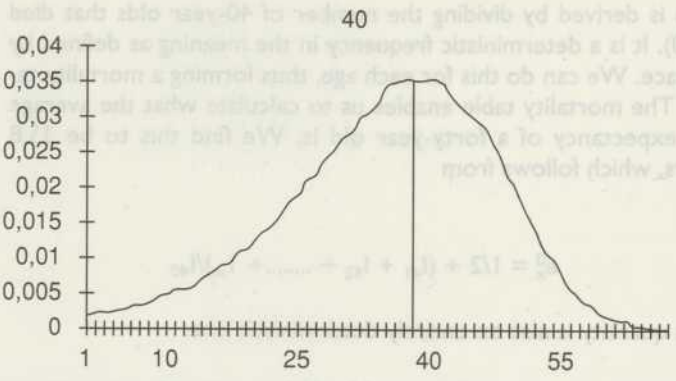


Illustration 2

Such lines can be drawn up for any age. They are not identical for each age, they change gradually. This is shown in the graph above (Illustration 2).

The same applies of other types of insurance; here was also first (looking at disabilitytables, tables of medical costs, etc.) a similar breakdown for each age bracket.

What does the insurer do with such a breakdown and why does he not confine himself to the average value? This average will surely work out if the group is large enough. It is th law of large numbers.

The insurer is faced with two problems in this context:

a) If there are too many applicants from the 'left' part of the distribution, the insurer is faces with too many risks which have an unfavourable impact on the average. The company cannot sustain the average premium and the result is an unfavourable position in the market; higher premiums in turn make it difficult to attract new candidates for insurance policies.

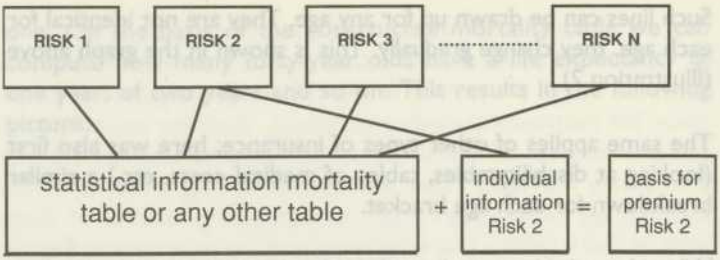
b) The insured himself may know (or possibly anticipate) that he belongs to the 'lefthand side' of the distribution; his risk is a poorer risk than the average. This may tempt him to insure more than he had originally intended. If this is true for life insurance (people taking out higher insurances) this could be even worse for other types of insurance in particular when the insured can influence the declaration of his disablement or illness.

The insurance company must guard itself against such cases, both in the interest of its competitive position in the market and in the interest of its other clients who will have to pay for the extra burden. The insurer has to make sure that it possesses the same amount of information as the client does (=equality of information).

This is achieved by examining the health of candidates. This is done with the aid of a health questionnaire which is filled out by the applicant.

Occasionally the answers warrant a physical examination; a physical examination is always required when large insured amounts are involved.

This following sketch indicates how the company gets the information:



Finally the premium may be (slightly) adjusted due to competitive influences of the free market.

The outcome of the individual information, the medical examination (or questionnaire) defines together with the statistical information (the mortality table or so on) the risk.

Why individual information?

Because it is very easy to write a health insurance when the ambulance is coming around the corner of the street, or to write a life insurance just before death is knocked on the door.

About the particular risk we can distinguished as follows:

– unavoidable.

– difficult to avoid, and

– avoidable.

or translated :

1. Unavoidable are inherent circumstances. Some people by nature are in better shape than others.
2. Difficult to avoid are external influences, for instance the place where one lives (air pollution) or works (handling certain substances, etc.)
3. Avoidable are behavioural circumstances such as smoking, alcohol consumption, etc.

Insurers cannot take this approach into account, because they have to set a reasonable and fair premium. Of course they will do what they can to attract as many applicants as possible; it is their business. In this respect changes have taken place. In the past the companies were inclined to ask an additional premium or even to decline the application/conditions, but gradually the

requirements have been set at the lowest level possible so as the offer insurance to a maximum number of people. This is the goal of the insurance business.

Generally speaking it may be said that filling out a health questionnaire or submitting oneself to a physical examination presents few problems; even an unfavourable outcome won't be regarded negatively, because people understand the rationale behind it.

Sometimes such a medical examination has an additional positive effect for the applicant, that is if a specific disease of discovered in an early stage. Naturally this may also have an unpleasant side, namely if the person involved is confronted with a disturbing finding.

We already noted that the medical examination is just a picture at a given moment. It is taken at the moment that the insurance is taken out. The medical adviser tries to link this to the best possible conclusion regarding the future. That future is different in character for various types of insurance. Concerning whole life insurance the medical adviser will have to estimate the chance of premature death; for disability insurance a prediction has to be made as to the ability to work and this up to a certain age. In case of illness it is different again. Someone may cause high medical expenses and yet be able to work and live to reach old age.

Usually the estimate by a medical adviser will be such that an actuary will translate it into a higher mortality risk, higher probability of medical costs, etc.

The actuary assumes that any abnormality in question will lead to an increased risk for the entire life span of the insurance. If we project this on the picture of the distribution for each age (Illustration 3), the calculation of the (increased) premium will be done along the line (a).

In some cases, we possess such extensive experience with specific abnormalities (knowledge specially accumulated by reinsurers) that a separate mortality line can be constructed for specific abnormalities. Generally the deviating line (a) will run approximately parallel to the standard one.

Can one alter this situation?

If the person involved is convinced that the reason for his premium increase no longer exists and that his life expectation is back to normal, he will apply for a re-examination. Sometimes

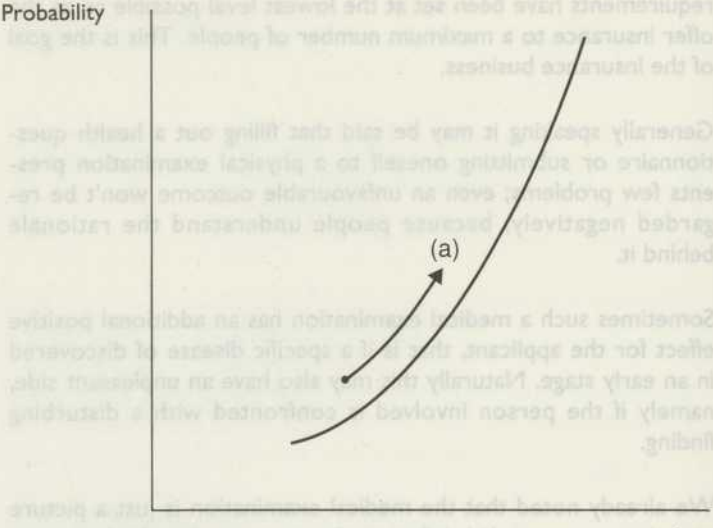


Illustration 3

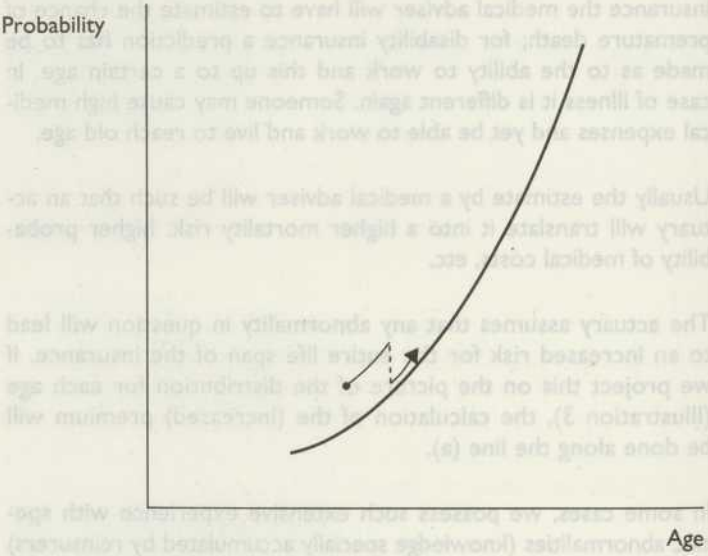


Illustration 4

this right has been agreed upon beforehand (e.g. after some years) but sometimes it has not. If a re-examination is done and the life expectation is back to normal, the relative mortality line will bend towards the normal one (Illustration 4).

Should the health of the person involved further deteriorate, even by his own fault (avoidable), this does not affect the pre-

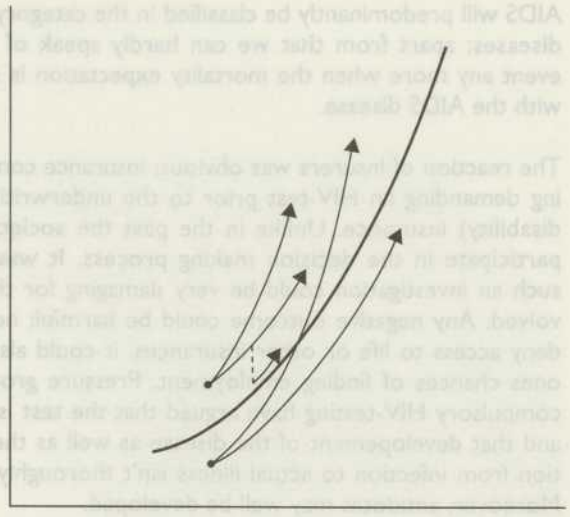


Illustration 5

mium setting. The same applies to someone who starts at the 'right-hand side' of the distribution. Under the influence of bad habits he may turn into a poor risk; his particular line will start to cross the normal one. This does not affect the premium either (Illustration 5).

Another problem arises: the insurer tries to set the premium as fairly as possible; he does so in such a manner that the insured do not have to carry the burden of additional solidarity for each other, an additional solidarity they never asked for. Yet carelessness and bad habits create a degree of unwanted solidarity. That rises the question whether a conscious deterioration of the state of health insurance the question arises whether others have to pay for the extra risk p.e. in connection with top sports). This runs parallel with common practice in general insurance where an increase in risk results in a new and higher premium.

So far the situation until recent times.

This picture has changed recently when insurers were faced with the phenomenon AIDS. Suddenly the mortality risk for certain age brackets increased considerably. This made no difference for those already insured, as we have seen above, but it was a different story for new insurances.

Insurers, just like anybody else, have no experience in dealing with AIDS, but it is assumed that those infected by the AIDS virus will in due course develop AIDS and the consequences thereof.

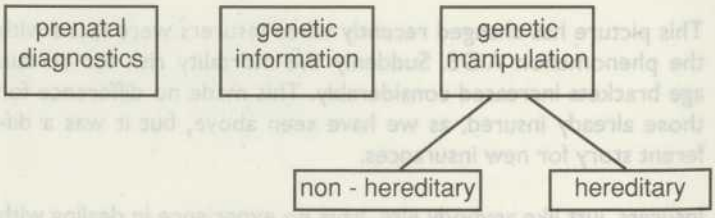
AIDS will predominantly be classified in the category of avoidable diseases; apart from that we can hardly speak of an uncertain event any more when the mortality expectation is so evident as with the AIDS disease.

The reaction of insurers was obvious: insurance companies starting demanding an HIV-test prior to the underwriting of (life or disability) insurance. Unlike in the past the society themselves participate in the decision making process. It was argued that such an investigation could be very damaging for the person involved. Any negative outcome could be harmful; not only can it deny access to life or other insurances, it could also ruin someones chances of finding employment. Pressure groups opposing compulsory HIV-testing have argued that the test is not infallible and that developement of the disease as well as the transformation from infection to actual illness isn't thoroughly understood. Moreover, antidotes may well be developed.

This evidently put the insurance industry in a quandary. On one side of the argument there is the public opinion opposed to testing yet on the other hand the companies must adhere to sound business management. In the Netherlands a solution was found in the form of a compulsory HIV-test for larger risks. The future will show the extent of losses incurred by the insurance companies.

Virtually at the same time the opportunities of genetic information emerged and more than a few people started to link these two events. There is no actual relationship: AIDS belongs to the category of practically avoidable diseases (so why should others contribute to the costs involved); genetic abnormalities are inevitable, they are built in genetically. Society focused on the similarities between the two such as privacy, the confrontation with unpalatable facts, social consequences, etc.

Why is genetic information interesting from the insurers point of view? As far as companies are concerned genetics are divisible into three subjects:



What is the importance of each of those parts?

This subject is the most developed of the three. It is of utmost importance to those involved. It is of less importance to insurers. Based on the assumption that these diagnostics provide us with an accurate prediction whether a child will be born with of without defects and if we assume that the parents are entirely free to decide whether they want the child (in this scenario society accepts the coinciding high expenses) the consequences are as follows:

If a decision is made in favour of abortion, the coinciding expenses will be paid by the healthinsurer. The other side of the coin is that the medical expenses for an ailing child will in all probability be many times higher. To underwrite such costs in health insurance is appropriate, and of course morally accepted.

If the parents consciously decide to accept all medical expenses for the child that child will be born by the insurer. It seems fully justified to make the other policy holders contribute (solidarity), because otherwise the free choice of the parents is jeopardized. This is what we are seeing in the Netherlands and other european countries. An opposite situation we find in the U.S. where parents come under pressure for abortion, while the child cannot be insured. These prenatal diagnostics are not of practical importance for life insurance and disability insurance; disabled children have no purpose for such insurance.

Genetic information

By far the most important part of genetics, for underwriters, is the use of genetic information. This information becomes available during a person's lifetime. The importance is underlined by the fact that insurance can only exist if the underwriter has sufficient information at his disposal. Genetic information means additional information, obtained from a genetic source.

First I would like to mention that insurers already possess a certain amount of hereditary information. The medical questionnaires include questions about illnesses of ancestors. The stardard procedures allow us to assess what the chances are that the person in question will contract hereditary determined diseases. The insurer is currently not entirely uninformed, although the information is rather rough. Therefore the question arises: does genetic information provide additional information?

The popular answer to this question is that in time we will all receive a genetic C.D., a genetic portrait or as we say in the Ne-

therlands a 'genetic passport', stating exactly which diseases we will contract and what the chances are of developing such illness. Barring accidents this knowledge enables us to plot our course through life. Of course people fear that insurers will use (or rather abuse) this to form an exact idea of the life expectations of the person in question. Is this depressing picture of the future correct?

Since it has been discovered that the genes are made up of DNA, are responsible for the heredity of certain diseases and that these genes are located in certain places of the chromosomes, research has endeavoured to analyze which genes are responsible for which diseases and has tried to pinpoint their exact location.

In depth exploration and analysis of the human gene is currently underway. This huge task has only just begun and although modern technology will enable us to speed up the pace, we must realize that it will take quite some time before we can map all human genes.

Assuming that we succeed in mapping all human genes, we can apply our knowledge to any individual's genes. If we would have to proceed with present day technology such an examination will prove to be a cumbersome task, probably only useful in very specific situations. A so called 'genetic passport' therefore seems unlikely, unless of course future technology would lend us a hand.

What information will be available?

To begin with we should make a distinction between diseases depending on the number of defective genes involved:

a) Diseases caused by one defective gene, e.g. Huntington's Chorea.

b) Diseases caused by a combination of defective genes; these may be differentiated according to the amount of genes involved, i.e. involving 2 genes or 3 genes etc. Very little is known about these so called multi-factorial diseases.

Genetic examination with respect to disease depending on a single defective gene will almost certainly provide relevant information. The outcome is that one will either develop the illness or one won't. This of course seems to be a sound conclusion, although it may not be possible to predict the onset and severity of illness in time. With such detailed information on hand the underwriter can't possibly provide the insurance this is contrast with the old situation where only heriditary information was

available (this probably involves diseases that can't be insured anyway, although –expensive– solutions have been found in a limited number of cases). In the new situation it is an acceptable risk or an unacceptable risk.

When more than one defective gene is involved, the case becomes rather complicated. It might be possible to predict the chance of illness as long as its occurrence depends on no more than two defective genes; information concerning the prospect of illness involving three or more genes, may be of very little value of the insurer. If for instance genetic examination were to disclose that the likelihood of a person's contracting a disease were 35% instead of 25% based on the subjects' previous records, than our overall knowledge hasn't notably increased.

Therefore, from an insurance point of view, one must seriously question the relevance of information on multiple defective genes. Nevertheless it seems likely that in certain intances we can augment the accuracy of our risk assessments.

It is this aspect that public debate focuses on. The public is inclined to believe that genetic information is essential and that such information may lead to more accurate risk assessment (higher premiums or rejections) than is the case at present. This in turn would lead to all sorts of social consequences: it may cause difficulties in finding employment, or obtaining a mortgage.

Based on this knowledge certain groups in society have urged that genetic information should be disclosed only to the subjects themselves and may only be applied for medical purposes. This movement regards genetic information as particularly privacy-sensitive; it is their conviction that a person can never be forced to participate in genetic testing, if the person does not want to do so (the right not to know). Others content that this situation would lead to inequeal information and thus have unacceptable consequences with respect to solidarity. The situation would ultimately cause disruption of the insurance industry. The champions of the privacy aspect sometimes take an even bolder standpoint. As noted before, they are apprehensive of the idea that insurance may be refused and are worried about the social consequences. On the other hand they are well aware that too much privacy is the key to misuse (inequality of information enables subjects to take advantage of the situation at the expense of others).

Proponents argue that insurers should be prohibited to gather any data at all whenever essential forms of insurance are con-

cerned. These forms of insurance ought to be available to everybody regardless of circumstances. The trouble with this idea lies in the fact that only politicians can decided on what forms of insurance are essential or not; this in turn will create an undersirable situation (it may obstruct the correct calculation of premiums due to influences from undesirable elements of solidarity, p.e. waiting to take a life insurance just before death).

Besides, there is a wide degree of variation between various types of insurance which we must take into consideration. With regard to health insurance the idea seems reasonable (it is in fact often the case): health insurance is practically essential (in view of the high costs hardly anyone can afford not to be insured), and it is practically impossible to influence the payments (claims). Here again a remark on the U.S. situation, where some 15% of the population is not insured for health care costs. However if we take life insurance or disability insurance into account, the case becomes different. Here the extent of indemnification (the amount of money) has been agreed on beforehand; furthermore not everybody needs to be insured (doesn't even want to be insured). Fraud is likely to occur much more often if insurers are obliged to underwrite all risks whilst the client have no actual obligation to take out insurance.

Equality of information is the obvious goal of insurers, except when it is unnecessary (as in health insurance). This means that an applicant must surrender all information he or she has acquired with regard to genetic examination to the underwriter, yet that the underwriter may not seek to iniate compulsory genetic examination.

It is here that I wish to speak of another aspect. It is not unlikely that illness will become manifest, where genetic factors are to blame in conjunction with certain negative habits (for instance living or nutritional factors). As I said earlier, changes in the individual's living habits do not influence the premium that the individual is paying for his policy. This observation usually pertains to changes for the worse.

We may now see the reverse. Knowledge of your genetically determined susceptibility may prompt you to change your way of living. Today smokers aren't entirely sure that smoking is harmful (apart from the rule of the thumb: smoking is bad for your health) because the smoker is unaware of his or her (potential) genetically determined susceptibility to lungcancer. If the person in question is aware of a high degree of susceptibility to lungcancer then one can ask: shall he or she continue to smoke? This of

course raises the opposite question: will a non-smoker who learns of his low genetic susceptibility to lungcancer, decide to start smoking?

The answer to the next question is essential: given that people have knowledge of certain genetic information, will they adjust their way of living accordingly? And that is of major importance to the insurer. Too much attention has focused on claims concerning whole life insurance (whereby premature death is a disadvantage to the insurer), yet the vast majority of insurance policies concerns old age pensions (i.e. long life risks). If people start to adjust their way of living in accordance with their genetic information, then we must not overlook that people will be aiming to increase their average age, which in turn has severe financial consequences for pensions.

A longer lifespan induced in this manner should be welcomed and it seems evident that all forthcoming costs should be paid for. Again the question arises: who is going to pay, how far can solidarity be stretched and should we occasionally adjust premiums accordingly? If behaviour is of such importance, the question arises whether or not the right premium may (must) also be adjusted during the term of the insurance.

Finally, a few words on genetic manipulation; this subject remind us of a science fiction-like world. The political forefront should stay on the alert. Still, we must make a few distinctions.

Suppose one has a defective gene, which in time is likely to cause illness, and this defect can be 'mended'. Possibilities of such repair are of the utmost importance to the person in question, because it will relieve the person of the disease and its consequences.

Here we must stress two aspects: such 'repair' can be costly, costs which will have to be reimbursed by the health insurer. This seems quite justified, just as the resulting solidarity. The risk of disability will decline, thus causing the product to become cheaper, which of course must be recommended. As far as life insurance is concerned: the repair case will prolong a person's lifespan, and this of course had consequences for old age pensions. A development we pointed out earlier on.

What remains to be discussed is the genetic manipulation with distinct hereditary components ('tampering with genes'). Whether or not this is of any consequence for underwriters cannot now be determined. Right now it looks more like a social and political problem.

In conclusion we can state:

It is highly doubtful whether genetic information will be of any use to insurers.

Should genetic information prove to be of value, then we must maintain the principle of equality of information, except for types of insurance that the entire population depends upon and where fraud is practically impossible, as is the case in health insurance. The insurers will not initiate compulsory gentic examination.

Should genetic information prove to be of importance, then we must realise that people will adjust their way of living accordingly. Not only will this influence the insurance industry, but it will also influence many others (e.g. food industry).

Both the opportunities of prenatal diagnostics and the 'mending' of genes should be recommended, although we must give serious thought to the consequences.

All in all it is not impossible that genetic research will pave the way to a better health future, regardless of the controversy surrounding hereditary genetic manipulation.

Finally some impressions on the situation about this topics in several countries.

Practically in all countries it is now more or less under discussion. Mostly there is a tendency to keep genetic information confidential for the person itself only. The argument: misuse by insurers, employers and so on.

First a remark about confidentiality. Confidentiality is primerly preferred by people with a bad genetic portrait. It is the same as asking for solidarity, which is also only preferred by the receiving party. But it is not only confidentiality, it is what people are doing with their genetic knowledge. When he or she has a good portrait, will he or she try to get a good job or to buy a low-priced insurance?

About the misuse two important remarks should be made:

1. In this argumentation no distinction is made between monogenetic and multifactorial deseases, while the information is totally different: monogenetic (practically) yes or no, multifactorial: a probability (at most).

2. No distinction is made between several different types of insurances, or other uses such as by employers.

In the U.S. we know the proposals of the Human Genome Privacy Act, which gives individuals the right to privacy on genetic information. Also no information to insurers, employers, etc. Congressional hearings will begin next spring.

In full contrast with this proposals we find in Germany a proposal for law that contains exactly my opinion, with the addition that there is no obligation on information for health insurance.

THE HUMAN GENOME PROJECT AND LABOUR RELATIONS

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ABSTRACT

Undoubtendly, knowledge of the Human Genome can influence the world of work if it provides information on the tendency to develop diseases in a certain environment or on the individual's aptitude for work, to give a few examples. The use of this type of genetic information may lead to legal problems if one considers who is the beneficiary of the information. However, analysis of the Human Genome would not be the only cause for this type of problems. At present, there is a company policy that controls access of a worker to the company by means of physical and psychological tests, the State itself makes use of these tactics for certain work activities.

THE HUMAN GENOME PROJECT AND LABOUR RELATIONS

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ABSTRACT

Undoubtedly, knowledge of the Human Genome can influence the world of work, if it provides information on the tendency to develop diseases in a certain environment or on the individual's aptitude for work, to give a few examples. The use of this type of genetic information may lead to legal problems if one considers who is the beneficiary of the information. However, analysis of the Human Genome would not be the only cause for this type of problems. At present, there is a company policy that controls access of a worker to the company by means of physical and psychological tests, the State itself makes use of these tactics for certain work activities.

1. The analysis and evaluation of the incidence of the genome project for labor relations has to be based on the current status of scientific research and, at most, on scientific hypothesis that are likely to be attained within the near future.

2. Quantitatively, human genome knowledge offers little information of actual relevance for labor relations. It's likely that genomic analysis may provide in the future more relevant information (for example, tendency for develop diseases by exposure to the enviroment, sterility in women or genetic markers associated with working aptitudes or ineptitudes).

   This information, certainly, might be important to select new workers or, later, to move the worker geographically or functionally within the company.

3. I will not consider here the labor consequences of genetic manipulation, because this aspect exceeds the labor-juridical area, falling in the realm or ethics and politics.

4. The main legal problem that the genome may pose in the future labor relations is, doubtless, that of possible use of the information provided. By hypothesis, the information derived from the genome may be used in the benefit of the worker, his owner; in the benefit of other workers and third parties outside the company; in the benefit of the comapny itself; and in the benefit of the general interest of the State. So, there would be four potential interests playing its role.

5. The worker might use this information for professional orientation, as a merit for being selected for a job or for promotions, and to avoid certains changes in the place or function of his job.

   Other workers and third parties might use this information to avoid risks derived from the actions of somebody potentially incompetent of dangerous. The company might use this information to justify discriminations in selecting workers or in assigning them certains tasks.

   Finally, the State might us this information in the interest of health preventive protection.

6. Some of these interests can become rights without major problems. This is the case with the interest of the worker to use genomic information to help him to choose and find a job.

   But, even in this case, some problems could appear as derived from the fact that voluntary allegations as a merit for being selected for a job or for promotion might suppose a factual and indirect pressure for those others who wouldn't

to adduce it because of its negative effect for them, as they would probably be rejected by the company in use of its contractual freedom.

However. I don't think that this simple fact will in the future determine a prohibition for those workers who voluntarily want to use the genomic information in their own interest.

7. Nevertheless, other interests may pose greater problems to become rights. This is the case in the interest for health of other workers and third parties "versus" the interests for privacy, to work and non-discrimination of the worker.

Doubtless, the information derived from the genome –as the information derived from any other way (the clinical history, for example)–, is within the ambit of the basic right to privacy of the worker and, so, it is necessary to respect it.

Although no right is absolute or illimited, the potential or tendential character of the information derived from the genome appears, in my opinion, not to be sufficiently solid to limit the basic rights of the person.

In fact, it's worth mentioning that the information about the tendencies to develop diseases by exposure to the environment or working aptitudes or ineptitudes provided by genome in the future will be always potential or tendential. So that working aptitudes or ineptitudes must be shown after an apprenticeship and the working experience; and the diseases with the monogenetic exception, can develop or not in contact with some environment circumstances.

8. The legal recognition of the interest of the company encounters similar problems of conflict with basic rights of the worker.

The company could adduce reasons of productivity to contract the best worker in order to justify the worker exigence of a genomic information in the contract moment or later on.

Certainly, in a democratic society, the company power brings about necessarily some limits, as the respect to he human basic rights and, among them, the right to privacy and the right of non-discrimination by intimate known facts.

Thus, I don't think that the simple managerial interest to the best contract could justify by itself the intromission in the worker privacy asking for a genomic analysis.

Nowadays, however, there are several managerial practices in order to claim, before the contract, some controls and

physical and psychological tests to check the conditions and aptitudes of the candidates to work.

In my opinion, the legal answer could be this: not every managerial practices are legal from the point of view of the human basic rights. It's necessary a reasonable relation between the information claimed and the task to do. For example, it would be legal a visual control of lorry-driver or the whole physical control of a football-players but it wouldn't be legal the exigence of some information about the sexual life of a miner candidate.

In this way, could be justified certains exigences of information about genetic aptitudes; perhaps, but more difficult, about the tendencies to develop diseases; but, absolutely, not about the women's sterility.

9. Finally, the legal recognition of the interest of the State in the benefit of health necessarily represents an injury to the rights of the worker, which are therefore "colonized" –as it is said– by the State.

Nowadays, the State stablishes the physical and psychological conditions of the worker for certains jobs (nuclear energy workers, for example)

The use of information derived from the genome would not be, therefore, a qualitative policy change, but only a further scientific refinement in the instruments of control.

10. In sum, two conceptions or positions of law policy will likely be confronted: 1) The first: the genome is entirely private and can oly be used for self-benefit. 2) The second: the information derived from the genome belongs to the collectivity and may be used for the collectivity benefit.

There is no doubt that intermediate positions will likely dominate in the future, rendering possible the reasonable use of genomic information in the interest of the company, in the interest of third parties and in the general interest represented by the State. Relativity is the conclussion.

Thank you

ETHICAL ASPECTS DERIVED FROM COMMERCIAL APPLICATIONS

ETHICAL ASPECTS DERIVED FROM COMMERCIAL APPLICATIONS

THE COMMERCIAL ASPECT OF DIAGNOSTIC TESTING

Helen Donis-Keller

Dept. of Genetics, Washington University Medical School, St. Louis, Missouri (USA)

ABSTRACT

Clinical diagnosis uses, amongst others, two types of tests: linkage tests for congenital disorders and ADN diagnostic tests to determine propensity to illness. The former study the genes of the illness and there are currently any norms for carrying out these tests. Besides, they give rise to errors on account of the order and distance of the genetic markers with respect to the gene of the illness.

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Clinical diagnosis uses, amongst others, two types of tests: linkage tests for congenital disorders and ADN diagnostic tests to determine propensity to illness. The former study the genes of the illness and there are currently only norms for carrying out these tests. Besides, they give rise to crises on account of the order and distance of the genetic markers with respect to the gene of the illness.

This cartoon depicts at least what some people might think is the ultimate in commercial diagnostics. This will probably horrify some of you, but why? First of all, at least for the Americans in the audience, I think there is a basic distrust in the US of Corporate America. Secondly, this cartoon implies that there is no physician interface between the patient and the diagnosis. Then third and perhaps most important: how feasible is it to do any of the tests that are shown here on the sign?

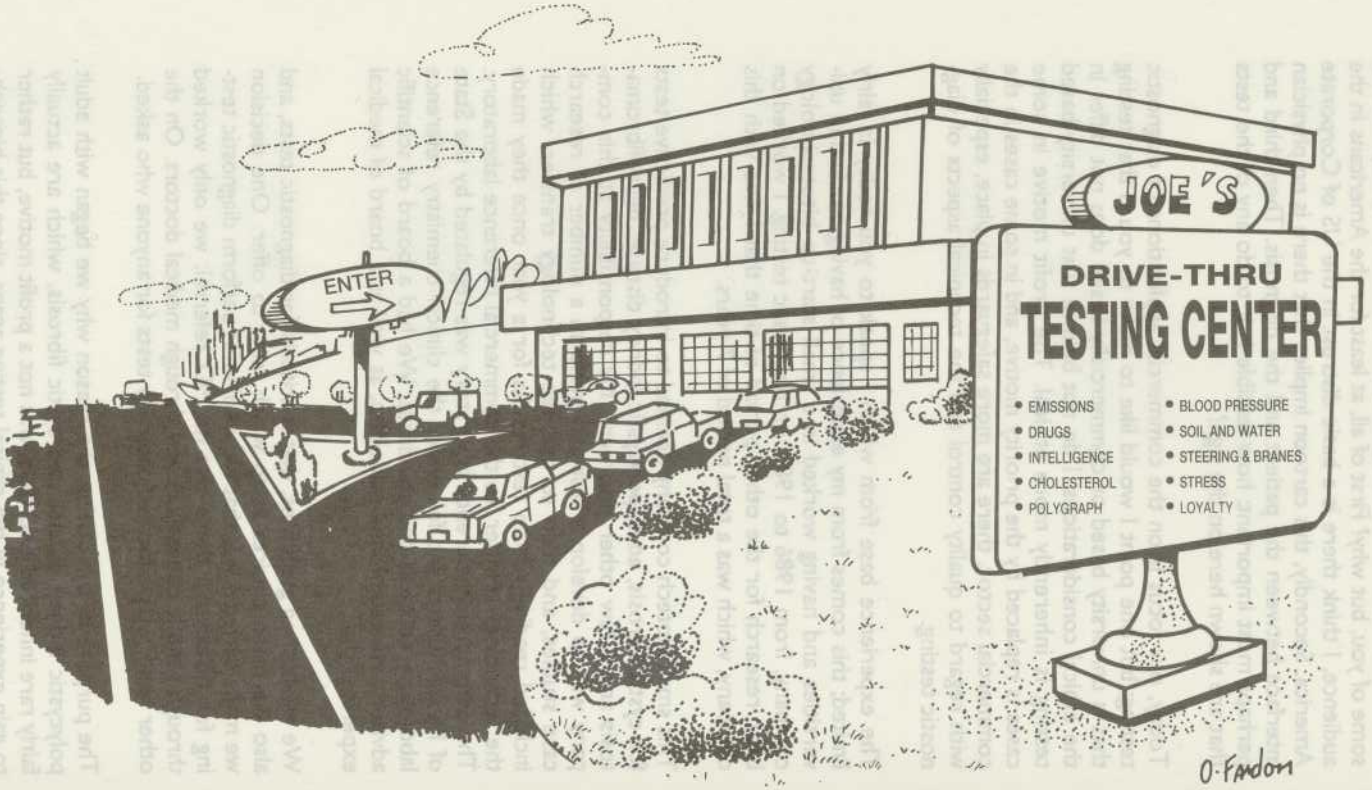
Today, our focus is on the commercial applications of diagnostic testing; but one point I would like to make to you is that testing that is university based or commercially based does not differ in the ethical considerations. I do not believe that university-based testing is inherently more ethical. The profit motive in some cases is replaced by the priority motive, and in some cases in the commercial sector, there are more safeguards in place, especially with regard to quality control and the technical aspects of diagnostic testing.

The experience base from which I speak to you today is fairly limited; this comes from my experience of having worked in universities and having worked in a small start-up bitotechnology company, from 1986 to 1989, on diagnostic testing. I worked on basic research for the other period of time that I was with this company, which was a total period of 7 years.

This small biotech company decided to introduce predictive tests for cystic fibrosis, adult polycystic kidney disease, neurofibromatosis and a few other disorders. My responsibility at this company was to develop a test and perform a number of research case studies, and then to oversee technology transfer, which included reading all the test results for a year once they made the technology transfer, to the commercial reference laboratory. The commercial reference laboratory was regulated by the State of Massachusetts and fell under the clinical chemistry reference laboratory controls and standards. We had a board of scientific advisers, we established guidelines, as well as a board of medical experts.

We established guidelines, that is criteria for diagnostic tests, and also we made choices as to which tests to offer. One decision we made early on was that we would not perform diagnostic testing for diseases if there was no MD referral; we only worked through genetic counsellors and through medical doctors. On the other hand, we performed paternity tests for anyone who asked.

The purpose of the testing, the reason why we began with adult polycystic kidney disease and cystic fibrosis, which are actually fairly rare inherited disorders, was not a profit motive, but rather to gain experience in the clinical testing arena, since this biotechnology company had no prior experience, with the long-terms goal of testing for more common disorders. I think my experi-


ENTER
JOE'S
DRIVE-THRU
TESTING CENTER
• EMISSIONS
• DRUGS
• INTELLIGENCE
• CHOLESTEROL
• POLYGRAPH
• BLOOD PRESSURE
• SOIL AND WATER
• STEERING & BRANES
• STRESS
• LOYALTY
O-Fardon

ence is probably typical of anyone working in a small biotech startup company, and Jack McConne I think will give you the perspective of someone who worked for a very large, well-established company –Johnson & Johnson. So I would like to review first the types of diagnostic tests and then focus on one type of test which we implemented.

First of all, there are genetic linkage tests for inherited disorders; in these tests we follow disease genes using genetic markers. We require at least one affected individual in a suitable family structure, and these are the tests that I will be talking about today. There are direct tests, using DNA analysis, permutations that are responsible for the disease; Norman Fost will focus on this aspect for cystic fibrosis.

Then there are DNA screening tests for disease susceptibility. The company I worked for decided not to offer tests of this type; these are population-based screening tests, and at the time we were considering them, there were tests that were being offered for atherosclerosis, emphysema, diabetes susceptibility, but we made the decision not to offer these types of test.

Then there are DNA fingerprinting for gentyping tests, that are applied for forensics purposes and parentage testing. The company I worked for decided not to get into the business of performing these tests for forensic purposes, mainly because the FBI entered the testing area and had decided themselves to set up testing for forensic purposes. So our company supplied the reagents for the FBI in order to perform these tests. There are several people in the audience who I think have much more experience with this type of testing –Don Rufo and Eric Lander perhaps will offer some comments at the end.

There are ethical concerns of course with this type of testing; one is the source of error in the tests, and the interpretation of results. I am sure you are all aware of the unscrupulous companies who by ineptitude, or simply lying, have really darkened the name of DNA testing. And of course, one of the main problems is our judicial system and not so much the error rate in these tests, because it is based on winning and not on getting at the truth; the major objective of defence and prosecution is to discredit expert witnesses, and I guess we should not forget that we are participants in this, willing or unwilling.

Here are the issues to consider. What are the criteria for high quality diagnostic tests? And the main point I want to make is that determination of a high-quality diagnostic test is in itself an ethical consideration, which I think is not being addressed in the academic or commercial communities today with regard to DNA testing. There are no uniform standards that have been established in any form for the linkage based tests I will be discussing.

Secondly, quality control; there are a lot of labs offering tests. There have been some attempts to set up standards in the commercial sector, but there has been no agreement on, for example proficiency testing.

A third point is record-keeping, and this has several dimensions. First of all, sample-tracking. The samples that are obtained for these tests are often and almost always obtained at some distance by people not employed by the company or the universitiy, then the samples are sent to where the test performance is done. This is probably the main source of errors that occur; sample mix-ups, sample mislabeling at the point, for example, where the blood is being drawn. But the questions are how do we track the samples? By name? By number? Every lab has a different way of tracking the samples. And secondly, how long should records be kept? This is an issue we never resolved at the company where I worked; we just kept the records and thought at some later point in time we would decide when to destroy the records. And another aspect of this is storage of the sample; invariably there was DNA left over after the analysis was done. Was it our responsibility to save that sample, to send it back to the originator? Again, this was unresolved.

Then the third aspect is, how public does one become with the number and types of tests that are performed? In our company it was decided that we would not make public the number of tests that we performed for any given disorder, because we did not want our competitors to know how badly we were doing.

Then there is the communication of results. To whom are the results given, and in what form? We had a written report form which we agonised over in terms of how easy it would be to understand what the risk assessment was, how much information could we give out, what was our liability situation. We often gave results out over the telephone to genetic counsellors. I think were naive initially, for example if we told them it would take about two weeks to get the results back (this was using a Shouthern-based assay) exactly 14 days from the later, call expecting the result because the patient expected it. Well, invariably things went wrong in the lab, we had to repeat assays; and so we found ourselves in a very difficult situation.

One thing we also did not do was verify that the caller should have the information; it would have been very easy for patients to pretend to be the doctor or counsellor and get the information themselves. It ended up not being a problem for us, but I can see that it would have been, perhaps.

And there is the issue of timeliness. Our technicians were not paid to work weekends because of the cost; often we would get samples in for an amniocentesis in which time was very much an element.

Then the most sensitive issue probably: the cost and profit, and who would pay for testing. I guess often in universities one does not consider the cost of the development of the diagnostic test, and the regulatory costs that are involved as well. In the cases that I was involved in, there was no profit; we weren't even trying to break even. He were simply trying to introduce the test. But it may interest you to know the company that I worked for considered it unethical that many universities were offering the test for free, which really meant that they were seen as competitors and really compromised the ability of small companies to get into the business.

Who can or should be tested? This was always left to the determination of a physician. In the case of linkage tests, of course, one has to have an appropriate family structure, and we suggested to genetic counsellors and physicians what the structure should be. Who has access to information?

... And the next point I think is a more serious ethical one. Often new information was developed as a result of the test that had not been sought by the originating individuals at risk or their families. For example we had a test come in for adult polycystic kidney disease. The lab technician received the samples and processed them and by the time the analysis got to me, what had happened was that a number of people who were at risk, who were not requesting information, had been tested and we had the result. We knew in some cases that people would be predicted to be affected; in this case we simply turned the information over to the physician; it was an honest mistake, they just sent in bloodsamples from everyone that came in that day from that family.

In another case we sent out an amniocentesis sample and a karyotype was done; this was standard practice by this secondary lab that we sent this sample to, but no-one thought to ask the pregnant women whether or not she wanted it done. What if we had found out something from having looked at those chromosomes?

Then in another case, we were doing cystic fibrosis diagnosis, and it became obvious that there was a parentage problem. This was a very late analysis that was done as an amniocentesis. We only had a few days to return the result, and I noticed the stated father was probably not the father. I communicated with the genetic counsellor and asked for a unblood sample from the father. Well, as it turned out, the woman swore that the father was as stated. Tested a few more probes and verified, to our satisfaction, that the stated father was not the father. So the only result we could give was that it unlikely that this foetus was affected.

And as I mentioned earlier, participation on family members is an important consideration in linkage-based tests. And at this

point I would like to emphasize the importance of the physician's attitude. For example, in the case of plycystic kidney disease, the nephrologists were very much opposed to genetic testing –they were not educated about the value of genetic testing– and in fact they were very proud of their surgical intervention procedures and thought there was no need for genetic testing. We also found, interestingly enough, that in the case of adult polycystic kidney disease parents were always willing to participate. They considered themselves responsible for their offspring and were very willing to participate in the tests and were very willing kidney donors. On the other side, there is sometimes coercion of the family members to participate in the test.

Finally, which tests should be offered? For our company there were strong economic considerations when we considered which tests we might work on. Should every company be committed to offer all available diagnostic tests? It is very hard to acquire experience and maintain competence while offering a large number of tests.

I would like to move then to linkage-based tests, to make my point again that the quality of the diagnostic tests is an ethical issue.

With linkage-based tests one uses markers to follow the disease gene. So you can see the prediction of affected abnormal or carrier status of the affected individual, necessary for the performance of the test for the at-risk individual shown as the question mark. Now the only problem with this of course is that there is recombination as chromosomes are passed on from parent to offspring, and you can see here the result: the child at the bottom has a recombinant chromosome. This is the source of the inherent error rate in diagnostic tests of this type, and it just shows you the result one would have if one used only one marker on one side of the disease locus. You would make the wrong prediction, the wrong diagnosis, based on following the inheritance of the marker: you would not have seen the recombinant events.

The second issue that is very important for linkage-based tests is informativeness.

The quality of diagnostic testing for this type of test depends on the informativeness of the markers and the genetic distance of the marker, from the disease locus, because the frequency of recombination is related to how close the marker is to the disease gene.

Sources of error, then, in the linkage tests are, first of all, incorrect marker order and distances: on assumes for the calculations to make a risk assessment, a particular order of markers with

respect to the disease gene, and distances of the crossovers, which is why markers on both sides of the disease gene are very important. And then of course undetected genetic heterogeneity: for so many of these disorders there is the possibility that different genes on different chromosomes can independently give the same phenotype. One has to ensure that sufficient testing for genetic heterogeneity in the population has been done: and then of course there are DNA artifacts; when one does a [Southern-based] test, whether or not the DNA has been digested on completion is critical. Contamination of other samples with the genomic DNA of the individual being tested, and in the case of PCR detection, amplification artefacts can be prevalent. Then of course sample mix-up, which I think is a major source of error in testing, and as I mentioned before, paternity not as stated.

These are my criteria for a high-quality test: First it is very important that the markers be very close to the disease gene, (within a few per cent recombination) and that the markers flank the disease locus that crossovers can be detected. That leaves the possibility of a double crossover, which is a very rare event. Second, the markers must be highly informative, otherwise I think you are really deceiving the people for whom you say you are providing testing. If in only 30% of cases you give back unambiguous answers, the test is hardly worth doing. An then again, reasonably rapid test performance and communication results are important: people expect to get the answer back the next day. Genetic heterogeneity studies, as I mentioned: and tolerating only a low error rate in these types of tests are also important issues.

I have raised some of the ethical considerations that are present in all of these types of diagnostic tests, and the underlying theme, is that there are no uniform standards that have yet been established. One can always say that competition, at least in a free society, provides the best service; the best tests will naturally come forward because there will be competition for them. But that is not always the case. Someone can do better marketing and there is a lot of trust in medical doctors, and that should not be understated.

BIOTECHNOLOGY

Eladio Montoya

Technical Dept. of the Quality of Life and Natural Resources, General Secretariat for National Plan I + B. Madrid (Spain)

ABSTRACT

Man's struggle against nature has given and is giving as a result the accumulation of toxic products with harmful effects, not only from the ecological but also the genetic point of view, for these agents are able to bring about genic disorders. The development of medicine during this century, apart from its beneficial effects, also entails a negative effect on human natural selection, in this sense, there has been an increase in the number of people who are bearers of transmissible genetic disorders. Biotechnology, considered as the third great technological revolution of this century, offers solutions to genetic disorders and environmental problems. However, with the use of products, biotechnology is not exempt from problems if it encourages a social imbalance between different countries.

BIOTECHNOLOGY

Elodio Montoya

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ABSTRACT

Since man started agriculture, fighting against nature has been a continuous task for humankind. This struggle has had deleterious effects on natural evolution, not only from a general ecological point of view, but also because of the accumulation of noxious agents, specially after industrialization. This, together with other natural factors creating human diversity, has lead to the accumulation of products that can induce genetic disorders. In the present century the tremendous development of medicine, which beneficial effects are beyond of doubt, has also had a negative effect upon the natural selection of humans, and therefore more and more people carrying transmissible diseases are now able to have descendants. Biotechnology is contributing to the right of all human beings to health, to have descendents, and a new era has opened this year with the possibility of performing somatic cells gene therapy. Antisense RNAs and ribozymes are also now considered as potencial therapeutic agents against viral, neoplasic or genetic diseases. On the other hand Biotechnology is also offering solutions to environmental problems by the use of selected microorganisms or genetically manipulated ones which, for instance, degrade toxic products, accumulate heavy metals or produce biodegradable polymers. Biotechnology is being considered the third great technological revolution of this century, after nuclear energy and the technologies of information and communication. In Western countries, Biotechnology is supposed to have applications to sectors representing almost a 20% of the gross national incomes.

In opposition with nuclear energy, technologies of information and communication and biotechnology have a better acceptance by the public opinion, exception made of those groups which promote a "return to nature". This acceptance, moves between the hopes and the fears, and depends mostly upon the individual benefits that biotechnology is offering, specially concerning health. Nevertheless, Biotechnology, like other technologies is not exempt of problems related to the use of its products. Issues concerning the delivery of genetically engineered organisms, patent protection of these organisms and social disequilibrium that these new technologies can promote between countries, are probably the most important aspects of the social ethics of the new biotechnology.

Here I am going to address only two of these items, nameiy, increasing differences between developed and underdeveloped countries and safety.

1. In underdeveloped countries Biotechnology has social and economic positive efects, improving the production of crops, fuels, food like milk, or providing vaccines against endemic diseases. Negative implications of biotechnology are the increase of the economic gap between North and South, due to the difficulties to develop these technologies by developing countries wich of course will increase the

debt in these countries. The figures will be aproximately the same for the knowledge of the Human Genome. Does this means that we shold stop increasing our knowledge to avoid to magnify these differences? Of course not. I would like to bring here the recent words of Dr. Mangwende, Minister of Lands, Agriculture and Ru al Settlement of Zimbawe addressing this subject: "It is totally naive and in fact foolhardy for anyone that we should stop the wheel of technological innovations because the outputs might adversely effect a group of people". It has been said many times that because of its very nature, information resulting from the Human Genome analysis should be in the public domain. As far as I known this was one of the points of the so called Valencia Declaration on the Human Genome Project, two years ago. This expresses the generosity that the scientific family has always shown. The problem does not lie in the knowledge of how genes are all put together or which is the base sequence in these genes, the problem is the technology that will be develop for and by the project. Among these new technologies, it is clear that informatics will be implemented and new methods for sequencing and new vectors for genetic therapy will be developed. These technologies will get applications to the diagnostic and therapeutics of human diseases of different origin, including cancer, and infectious deseases, and to many other biotechnological processes. At the present, 18% of the pharmaceutical market depends on biotechnology. This includes of course antibiotics, and represents aproximately 30 billion dollars. From these more than 400 million dollars are products derived from monoclonal antibodies. Actually the market of DNA probes is still low, aproximately 19 million $ but it is expected to increase in 1992 to 600 million dollars. The Human Genome Project will therefore implement evolving biotechnologies which will be beneficial for many productive sectors and for many countries. The transnational character of this project will, without doubt, benefit the dissemination of knwoledge and their profits. The transfer of these technologies should be done through the cooperation. FAO, UNESCO, WHO, and the European Community STD program are good examples of multilateral cooperative frameworks that should be implemented in the future, as well as bilateral assistance.

2. Safety. Until now DNA recombinant technology has been proved to be not only a safe technology but safer than previous ones. For instance endocrinologist can now treat children with Growth Hormone without having the danger of inoculating diseases, as it was the case of the human hormone. Vaccines, like hepatitis B can be obtained without manipulation of the virus. This safety is due to a great extent, to the careful way in which researchers have dealt with the problem. The Berg letter, Asilomar conferences or the NIH

guidelines, are good examples of the degree of responsability undertaken concerning this topic. Seeing the problem retrospectively, all this measures were perhaps excessive, and in consequence they have been progressively modified. On the other hand they have had a negative impact on public opinion, a fact that is very probably influencing negatively other initiatives, but I think that at that moment they were necessary.

Safety has special importance when we are dealing with species. Doctors frequently have to take hercio decisions concerning patients.These decisions affect the individual life, but decisions concerning, for instance genetic manipulation of plants, can affect the evolution of a whole specie, or an ecologic system. Therefore genetic manipulations that affect environment are to be undertaken carefully and studies of dissemination, propagation, etc... are needed, and biological diversity should be mantained. This contrast with the situation of gene therapy, where only individuals are the object of manipulation. Let us consider the most compelling topic concerning gene therapy: germ line of embryo genetic therapy. I am very sorry to say that for me there is no an ethic or moral problem involved, but only a problem of uses and safety. By now we are used to multiple surgical procedures, including grafts that increase life expectancy and quality of life of people carrying severe diseases. Procedures that modify the phenotype of individuals are also continuously performed and all these manipulations are well accepted by the general public, although they are painful, and some of them involve grafting of foreign organs and in some cases they are life threatening. So, why are they accepted? Probably because their effects are predictible and immediate, because they do not affect descendents and specially because they can be easily understood. People consider genetic modification as something mysterious that manipulates the very essential nature of man and his destiny, instead of considering it, when feasible, as a simple intervention for correcting the errors of Nature. Of course this is not the moment to perform such type of interventions, because in the present state of knowledge the results may be impredictible, but we probably should not close the door of terminal or embryo therapy for ever, and we shall consider the actual prohibitions in most legislations as a moratorium. Ethical problems will then arrive, for example, the right to patent vectors, which in some way could be compared to patent surgical procedures. Fortunatedly, in the future probably there will be no need for such manipulations, because very early diagnostic test of embryo, like it has been already started, will avoid other procedures.

I wish to finish by quoting samebody who has dedicated a great part of his life to Bioethics, Prof. Edouard Boné:

"Does man have the right to modify nature, to claim to correct or to improve it to 'arrange' the DNA molecule, artificially create new species, to attempt to change his own individual or specific identity? 'Doesn't Nature know best'? Might there not be a limit beyond which we risk everything getting out of control? And finally, do we demand that humanity, after having manipulated, altered, and experimented with everything in this world, stops in front of its own chromosomes, feeling that by crossing this limit it would make itself guilty of some unaccepted violation?" To this question, says Father Boné, "I would think that we have a valid and explicit answer in our present understanding of scientific evolution. Man, the thinking craftsman has as his privilege to decode and comprehend reality, to put his hand on what makes the world work, to take in hand the destiny and the competion of the planet and to exploit its resources...".

Thank you very much for your kind atention.

DIAGNOSTIC POPULATION

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DIAGNOSTIC POPULATION TESTING OF GENE CF

Norman Fost

Program in Medical Ethics,
University of Wisconsin Medical School

ABSTRACT

There are at present proposals to carry out genetic diagnostic population tests to detect bearers of cystic fibrosis.

In the author's opinion, almost none of these proposals follows widely consensed criteria at the institutional level, such as: adequate experimental design, proof of efficiency, study of toxicity and acceptability of costs. Therefore, these proposals require more detailed analysis before their generalized putting into practice.

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There is wide consensus on the criteria to be followed when carrying out programmes of genetic diagnostic population testing that are ethically acceptable,a consensus that seems to be reflected in the similar conclusions reached by the National Acaademy of Sciences, the Hastings Center and the American Presidential Commission for the study of ethical problems in medicine. Current proposals on the carrying out of wide-ranging diagnostic population testing for the detection of CF bearers (CF = cystic fibrosis), or diagnostic testing in new-born infants for pre-symptomatic treatment, follow practically none of these recommendations.

At present proposals for the detection of bearers should take into account the following problems:

1. The scant sensitivity of available tests (75 to 80%) will cause unsurmountable uncertainty in many couples, for one of the two could be positive and the other give negative results in the test without their genetic situation being known. If all pregnant women were submitted to the test, 200.000 of them would be in this situation, 97% of this kind of couple would run no risk at all.

2. The dilemmas posed to the counsellor are extraordinarily complex, and yet there is no infrastructure for expert counselling to be made available to patients. If all genetic counsellors with experience in the United States were recruited, and if they spent 10 minutes counselling each couple, each counsellor would have to devote 17 weeks to this task. Consequently, it will be non-qualified people who carry out the work of counselling.

3. The costs of diagnostic testing programme of this type would amount to over a thousand million dollars. The number of pregnancies terminated for this reason is unknown, but should they be reduced by 50%, costs would be more than 2 million dollars per pregnancy thus terminated. This may be hard to justify in a country in which 37 million people have no basic health insurance. Obviously, company interests and conflicts of interests are entailed.

4. The public is little disposed to participating in this type of programme: public opinion has little knowledge of cystic fibrosis and even the most elementary genetic information is barely available to the consumer. Therefore, it is likely that there will be great confusion and that decisions taken on reproduction will be somewhat irrational.

5. No pilot studies have been carried out on the efficiency and toxicity of bearers of cystic fibrosis.Therefore, these proposals are experiments that require analysis at institutional le-v-el, strict rules on the consent of the person informed and a

homologation of results, before it is possible to carry out testing on a generalized scale.

In Australia, Colorado and some other communities, diagnostic testing has been carried out on new-born infants for five years, as presymptomatic testing; yet in no case has either the experimental design, proof that efficiency and toxicity levels and costs are acceptable been adequate. In Wisconsin, an aleatory, controlled, prospective study has been carried out that has still not shown any medical benefit after five years, although this study has not yet been completed.

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LESSONS FROM THE PAST: PROSPECTS FOR THE FUTURE

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BEYOND DECLARATIONS: IS IT POSSIBLE TO FIT ETHICS INTO THE HUMAN GENOME PROJECT?

William G. Bartholome

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ABSTRACT

Knowledge can be used destructively for human dignity. What can be done to guarantee that genetic information is used exclusively to increase human dignity? It is assumed that the new genetic knowledge, as likewise technological progress associated with same, will be applied in a clinical context, although there is no mechanism to control this application.

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The title of my presentation was drawn from the document that was drafted here in Valencia in October of 1988. It is called the "Valencia Declaration on the Human Genome Project." As I read this declaration, I was struck with the fact that with one exception, which I will discuss in detail, most of the values informing the declaration where what might be called the values of good or ideal science: the assumption that the pursuit of knowledge is good; the values of collaboration and coordination and the value of honesty or disclosure of information. The exception is the acknowledgment that participating scientists have the responsability "...to help ensure that genetic information be used only to enhance the dignity of the individual." Although the declaration endorsed the Human Genome Organization (HUGO) as the: "lead body... to promote the goals and objectives addressed in this declaration," it is silent on the question of specific steps to be taken to achieve these goals.

As we have been told repeatedly in this conference, human history is replete with examples of the use of the knowledge of human differences –often nothing more than beliefs based on ignorance, prejudice or fear– to justify systematic violations of the welfare, rights and dignity of individuals, groups and whole societies. As we have been told, the history of human genetics more than explains the concern reflected in the Valencia Declaration that knowledge might be used in ways highly destructive of human dignity. What should be done to ensure that genetic information will be used only to enhance dignity?

One of the concerns that prompted me to accept the invitation to attend this meeting, is that the clinical geneticists I know and work with struggle to deal with the ethical ambiguity, complexity and conflicts involved in application of *existing* genetic knowledge and technology. In fact, the literature describing their on-going struggle with the demands of ethics contains little of no clarity or consensus about the meaning or demands of ethical declarations such as: "genetic information be used only to enhance the dignity of the individual".

Of proponents and supporters of the Human Genome Project are correct in their predicitions, it is likely that these efforts will exponentially increase the fund of basic information available regarding human genetics. It is also assumed that this dramatic increase will "pay off" in the sense of the application of this new knowledge to the development of a wide variety of genetic technologies and products.

In the second half of the title of my presentation I invocked the metaphor of knowledge and its development as a *building*. I asked "Can Ethics Be Built into the Human Genome Project?" I should have been more careful in my use of this metaphor. As reflected in the question I asked yesterday afternoon, I believe –and it is essential that we acknowledge here– that a wide range of values

and ethical assumptions have been "built into the Genome Project". My question shold have been: "How *Should* Ethics Be Built into the Genome Project?" Therefore, one of the first tasks must be undertaken is the identification and critical examination of the values that inform this project. I see the identification of these values as a fairly straight-forward task. By engaging in a sustained dialogue over time with members of the community of scholars doing-ethics –long after the conclusion of this conference– those of you who are undertaking this project could come to know the often hidden values that inform what you are doing.

It would then be necessary for you to "build into" your project a process by which these values would be subjected to critical examination and reformulation over time. Clearly the creators and masterminds of this ambitious project understood the importance of this effort. Many important and significant steps have been taken. Clearly the most visible steps in this regard are dedicated fiscal resources –we have been told this is to be at least 3% of the total funding; the establishment of the "Ethical, Legal and Social Implications (ELSI) Program"– *and* the recruitment of a highly qualified philosoper to manage the program. Eric, in cooperation with the Joint NIH-DOE Working Group, has undertaken important steps in the process of providing a mechanism for on-going critical examination of the genome projects from an ethical perspective.

In trying to prepare myself to have some practical suggestions about additional aspects of this process, I have consulted with Eric and other members of the clinical ethics community with much more experience and expertise than I in the area of genetic ethics. In the summary of my presentation, I have proposed a series of additional steps to be considered. I will not repeat all of them here. I would, however, like to specifically discuss there of them. First, I suggested that consideration be given to the establishment of what I called an "Ethics Board" to work with Eric and the Joint Working Group in the ELSI Program. It may well be that this could best be accomplished by an expansion of the membership of the Working Group to include additional voices in clinical ethics. My concern is that the decisions which guide the work of this program need to be informed by the critical perspective of scholars from the "outside" i.e. scholars in ethics whose work is constantly shaped by having to work in clinical contexts and by those whose work is subject to the scrutinty of academic peers.

I also suggested that consideration be given to the creation of what I called a National Consortium or Commission to develop and recommend appropriate legislation to prevent the inappropriate, non-clinical uses of genetic knowledge and technology; and to recommend appropriate legislation to combat genetic discrimination. Obviously, the model I had in mind in making that suggestion was that of the President's Commission. In fact, the re-

port of that Commission on Ethical Issues in Genetic Screening remains an important document in genetic ethics particularly as it relates to ethical issues in screening. I see the need for such a Commission to supplement the educational and extra-mural research activites of the ELSI Program. One obvious and pressing issue to be examined is the possible expansion of federal civil rights and disability legislation to include individuals who have been identified as "genetically different".

The third suggestion I would like to briefly discuss is that of creating a networking system for Institutional Review Boards faced with the challenging task of reviewing genetic research at universities and research centers. This might well be an international networking system tied administratively to the Human Genome Organization through its Ethics Committee. As the chair of my institutions IRB I have become acutely aware of the difficulty of providing adequate review of the complex ethical issues raised by these research projects. It is not possible for each IRB to have of develop the necessary experience and expertise in genetic ethics.

I would like to conclude my remarks about "building" ethics into this project with observations that deal with two other metaphors for knowledge that seem to have been operative in this workshop. One of the metaphors which appears to have shaped many of the presentations and much of the converstation at this conference appears to be the metaphor *knowledge as power.* In fact, one form of this metaphor appears to have shaped the decision to have the conference in the first place, namely that of *knowledge as weapon* or the even more dramatic metaphor of knowledge as cannibal or devouring monster, mentioned by Nancy Wexler yesterday morning. I would like to use these metaphors to express my concerns about what appears to be a very basic assumption which guides this project. It is the assumption that this new genetic knowledge and the technological progress its spawns will be used, ie. applied, in a medical or clinical context. It is assumed that it will be utilized by health care professionals working in clinical settings providing health care services to their patients. However, there is no existing mechanism by which the use of this newly developed knowledge and technology can be *controlled,* curtailed of limited to use in this setting. If the concern is that we do not repeat the experience of "our colleges in nuclear physics after the Second World War" we must critically examine this assumption. I hear you claiming that this project will produce or allow for the development of "powerful knowledge" and a vast armamentarium of powerful new technologies. Absent some as-yet-to-be developed mechanisms, this knowledge and technology will be used by those with power to increase their power. It will be marketed by its developers to the powerful –to employers, to corporations, to insurance companies, to law enforcement agencies and to governments. I would draw your attention to what has happened in the United States to the newly developed knowledge and technologies involved in testing human

urine and blood for organic chemicals– i.e. socalled "drug testing" and to the use of antibody testing for HIV virus to prevent the spread of HIV infection through the transfusion of blood. At the present time in my country the vast majority of drug tests and HIV tests are ordered by non-health care providers and performed on individuals who are not patients. I would also point out that one of major users of this knowledge and technology is the government of my country.

Another of the more prominent metaphors underlying this project is that of *knowledge as geography* –most vividly presented to us yesterday by Al Jonsen. Those undertaking the project seek to create a "map". With this map, they claim, we will be better able to "find our way" in dealing with human genetic difference and disease. Without this "map" we will be "lost" in ignorance on the unexplored genetic frontier. We will be left to continue to grope and stumble along without the knowledge this map promises to provide. With the map we will be better able to get where we want to be in terms of our ability to control, to prevent and to respond to genetic disease.

Yet it is not at all clear to me that we know where we are going. Do we know where we want to go? Do we seek to prevent all genetic difference? Do we seek only to prevent or respond to certain kinds or levels of difference? Which differences? Do we seek to prevent of thwart or even cure all genetic diseases? What goals shold inform this search, this quest? Who will determine which goals should be sought? If we do not (cannot?) know where we want to be of what use is a better map?

This geographical metaphor also invites us to attend to the important task of understanding how this journey fits into the larger context of humanity's historical quest.

What is clear to me is that the burden of human suffering in our world community is *not* caused most fundamentally by human genetic difference or even by human genetic disease. In fact, this burden is *not* caused by the lack of what those of us who live in privileged societies call medical care. Genetic disease may be the leading cause of of infant mortality in the United Kingdom, but it is *not* the leading cause of the death of infants and children in the world. The "map" we need to deal with the this globe's burden of human suffering is not a genetic map. If our goal is to find the way to respond effectively to the global burden of human suffering, this quest for a better genetic "map" must be seen as a distraction, a luxury, at best, a noble but certainly not essential human quest. When we take a wide-view –a world view– –a human community view– we see the specter of a crushing burden of human misery, hunger, homelessness and privation which characterize life for most of those in our global community. Will this project and its "new map" help us find the way in seeking to respond to these basic human needs? I do not find its potential for

human benefit –in terms of the common good of a community of nations– to be either obvious or particularly enormous.

Elke Jordan asked us to reflect on the question of what conception of the public good should inform NIH policies on data sharing by Human Genome investigators. Although this seems to be an appropriate and important question, its asking is also dangerous. As we seek to answer it and a host of related questions about the nature of the "public" or "common good", who is the "we" who will provide the answer? Whose voices will be heard as the answer to this question is formulated? I am concerned that our answer may well be just that "our" answer –an answer that fits the desires and needs of those of us who are privileged. Will it fit the aspirations and needs of the billions of those members of the human community not fortunate enough to participate in this dialogue?

I am also concerned that many so-called developed nations are alreaday struggling under the specter of a burden of biotechnology and the medical-industrial complex which supports and nourishes its relentless growth. In many countries, this monster already grows out of control consuming an ever-greater portion of the social resourses. Its growth has resulted in a widespread medicalization of human life in these societies and has distored social values, priorites and programs in pursuit of its utopian (some would say demonic) vision of a maximally prolonged human existence free of all suffering and disease. In at least one of these countries –my own– this monster has lead us seriously astray (we are indeed in need of a map, but not a genetic map). Even as Americans spend more and more hundreds of billions of dollars each year to feed the insatiable appetite for the latest in modern medicine, we must suffer the humiliation of calling ourselves a developed nation –even a leader in the world community– and yet we have no health care system; no system by which we can discharge our social obligation to provide health care to our citizens.

GENETIC INEQUALITY AND SOCIAL INJUSTICE: A LESSON FROM HISTORY

Benno Müller-Hill

Institute of Genetics of the
University of Cologne (Germany)

ABSTRACT

It is certain that the Human Genome Project will have social consequences. In Nazi Germany, there were attempts to apply human genetics with the aim of creating a superior, generically selected race. Illegal sterilization was a habitual practice and a law was defended that allowed euthanasia. But all this belongs to the past. At present, we live in a world in which a large part of the population has no housing, food or work, and within this context of inequality the Human Genome Project poses problems. How? It may be that genetic inequality is translated into genetic "injustice" and that this may justify social injustice.

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Introduction

The Human Genome Project is a great intellectual and technical challenge for those who like to work with DNA. One can safely predict that those involved will have little time to think about the possible problems the successful project will create for society. A scientist is after all judged for his scientific accomplishments and not for his worries about the possible misuse of science. So the proposal that about three percent of the bugdet of the project should go to experts –bioethicists– who make a living of thinking about such things makes sense.

My experience with bioethicists is limited to encounters at three conferences including this one. These encounters have been deeply disquieting for me. I liked of course the anglosaxon attitude that (almost) all fundamental research is legitimate (I share this view). But I dislike the corresponding view that (almost) all application to man and society is potentially legitimate too.

The most disturbing aspect is the apparent absence of any tabus. According to this view there is no proposition which can not be discussed carefully and all propositions are defendable as long as they are coherent. But what is true for science is –in my opinion– not true for the issues trascending science. So economic arguments should be *nil ab initio* when they violate human rights.

I will argue that something can be learned from history in this respect. Half a century ago, German human geneticists allied themselves with the antisemitic Nazi Party to propagate their common interest: to apply human genetics for the utopian goal of a world dominated by a genetically selected, superior nordic race.

A Short History of the Past of Human Genetics in Nazi Germany

It is impossible to present an adequate picture of the history of human genetics in Nazi Germany in a few pages. I would like to draw the attention of the international readers to some books dealing with the phenomenon [1-4]. For the situation in the US and England and some other countries see [5-7]. Here I can just summarize: In the twenties and thirties the evidence seemed to grow that most physical and psychic ailments had some genetic defect as basis. A large percentage of society seemed to be made up of such genetically afflicted persons. Furthermore the notion was advanced that these afflicted persons bred faster than those with intact, "valuable" genes. Biological evolution was seen as a process where dog eats dog and social evolution was seen in the same manner. A most readable story is told by an American pro-

fessor of zoology who in 1915 sat night after night in the German Army Headquarters in Brussels and talked with a German zoologist who had become an army officer [8]. The American arrived as a pacifist and left deeply convinced that the war against Germany was justified. A country where the intellectuals made sociopolitical Darwinism their religion had to be contained and, if necessary, by war.

The German human geneticists of the twenties had no connection any more to any religion. Darwinism was the surrogate they used. Thus they advocated that *they* should become the makers of human biological and social evolution. They proposed, as a first measure, sterilization of a large section of the German Population. In the Weimar Republic no party except the Nazis supported enforced sterilization. Even sterilization after informed consent was extremely controversial. It is thus not astonishing that almost all German geneticists prior to 1933 asked for sterilization with informed consent.

There was one party which openly said that informed consents was democratic nonsense and this was the Nazi party. In fact the Nazi party approached the leading German human geneticists in 1932 and were warmly received [9]. It is thus not astonishing that a close collaboration with the human geneticists began after the Nazis came to power in 1933. The geneticists asked for support of their research and got it amply. The Nazis asked for theoretical and practical support for their race measures. And they got what they wanted.

The human geneticists had to train the medical doctors who later became involved in the various racial measures. I would just like to list a few of these:

- The legal sterilization of about 350 000 German citizens according to the law of 1933 which asked for the sterilisation of schizophrenics, manic depressives, alcoholics, idiots and some others afflicted with rare genetic diseases.

- The nonlegal sterilization of all coloured German citizens.

- The nonlegal sterilization of almost all German Gypsies. Most German Gypsies perished later in Auschwitz

- The planned sterilization of all German citizens with "antisocial" behaviour.

- The planned sterilization of all "quarter-Jews".

- The expert opinion in all cases of questionable Jewish origin.

- The racial evaluation of the whole population in Poland and the Soviet Union.

- The framing of a law legalizing "euthanasia".
- The evaluation and killing of psychiatric patients after 1940.
- The life and death decisions in Auschwitz.

When the war ended in 1945 almost all German human geneticists and psychiatrists, professors and postdocs alike, were so deeply entangled in some of these actions that there were just two options:

- To continue. Then none of them would ever have to bear witness against any collegue.
- To close the fields of human genetics and psychiatry completely.

Here as elsewhere the first option became reality. The international community of human geneticists or psychiatrists prefered not to know –and when somebody did know, he kept silent and shuddered. The German anthropologist, human geneticists and psychiatrists continued to publish, meet and teach as if nothing had happened. There was not a single article or book on the history of human genetics during these years by one of its practitioners. Even those who had been in trouble in Nazi Germany kept silent for many years. Only in 1961 did Karl Saller, who had been dismissed as a lecturerer in 1935, dare to write his account on his former and present collegues [10]. His book made him promptly a leper among his collegues.

To illustrate the situation I would like to name just three of the speakers of the 6th Conference of the German Anthropological Society (6. *Tagung der Deutschen Gesellschaft für Anthropologie*) in Kiel, July 30 to August 2, 1958. Among the speakers are listed [11]:

- H. Schade on anthropological research in Macedonia: Schade was an SS officer and member of the SS race office. In this capacity he was active during the war in Yugoslavia. In 1937 he was involved in the illegal sterilization of coloured children.
- B.K. Schultz on inheritance of variabilities of the foot: Schulz was an SS general and head of the race buro of the SS. He became responsible for the racial screening in all of Europe in 1943. He was author of a proposal to head an office in which all "quarter-Jews" had to be examined for possible sterilization.
- H. Fleischhacker on bloodgroups and race mixing in El Salvador. Fleischhacker was an SS officer. In 1943 he selected 79 *typical* Jews in Auschwitz to be sent to the concentration camp Natzweiler near Strassburg. There they were all killed to be-

come part of the anthropological collection of the Strasbourg anatomy of professor Hirt.

The influence of all these geneticists and psychiatrists disappeared only with their retirement and death. This process had come more or less to an end in the eighties. Then suddenly a flood of articles and books appeared in Germany dealing with these human geneticists, anthropologists, psychiatrists, etc. The articles, most of them well researched, many in popular journals, completely destroyed the respectability of geneticists of all sorts. It was coincidental that some years earlier cloning of DNA was for a short time regarded as dangerous. This was simply too much for the German public. The old generation had objectively been involved in crime and what was the new generation doing? The very low esteem of the general public for genetic engeneering in all its forms results from this.

Lessons from the Past

The present situation differs from the past in essential points:

- In the past only phenotypes were available for evaluation. Now genotypes will be unambiguously determined.

- In the past the state and its agencies enforced sterilization, abortion and death. Now these decisions are left to the individual citizen.

- In the past knowledge about the presumed genotypes was freely circulated among the interested state agencies. Now state agencies are under control. But what about insurance companies and private business?

In the best of all possible worlds, which does not exist, where everybody finds employment, housing and health insurance, the Human Genome Project poses no threat. But in the US where about one percent of the population belongs to the homeless, where 37 million people have no health insurance, where the crowds of the poor and the jobless are growing, the Human Genome Project does pose problems. Here the economic pressure in immense that the insurance company may know the genotype to determine the insurance rate and that the company may know the genotype of its potential employee. I am afraid that such a situation where all is decided by consenting individuals under economic pressure, will push the US in the next half century in a situation resembling the science fiction novels of Philipp K. Dick. Social injustice will become first justified and later amplified by genetic injustice. The discovery that some unfavourable genotype are frequently found in certain ethnic groups will make racism again respectable. The end of this development can only result in

violent social upheavals to end or cement this state of scientific racism. This will also mean the end of respectable genetics because the geneticists will be unable to hide like their German colleagues did a century ago.

Since I find this development utterly undesirable I propose here again what I proposed in vain here and elsewhere [12].

1. Every person has the right to know his genotype in full, in part or, if he wishes, not at all.

2. The genotype of a person should not be determined unless the person has specifically asked for this. It should be a criminal offense to determine the genotype of a person without being authorized by this person. Exceptions as genetic fingerprinting should be carefully qualified.

3. Parents have the right to ask, or not to ask, for particular genotypes of their children, when the onset of the sickness brought about by the particular genotype is below the age of eighteen. They have not the right to ask for genotypes of their children if their genetic condition will not disable them before the age of eighteen.

4. Every pregnant mother has the right to ask, or not to ask, for the genotypes of the unborn. The genotypes of the unborn should not be determined unless after specific authorization of the pregnant woman. Insurance companies should not have the right to ask for the genotype of an unborn. Abortion should be decided by the pregnant women and not by another persons.

5. No third person, insurance company, employer and the like has the right to ask for the genotype of a particular person or to determine it. Breach of this should be made a criminal offense.

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THE INFLUENCE OF EUGENICS ON HUMAN GENETICS

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ABSTRACT

As from 1900, eugenics became institutionalized in several European countries and in the United States, However, thirty years later, it began to be criticized as a science because of its scant scientific consistency and due to social prejudices, although it continued to influence human genetics, particularly in the United States.

With time, biochemistry slowly gained ground within genetics, contributing scientific rigour to research; thalasemia and falciform anemia are two examples of this genetic research. Consequently, scientific rigor gradually supplanted eugenics, in any case, ethics must always be present and not only when applying a certain research but also when questioning the aims of research.

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With time, biochemistry slowly gained ground within genetics, contributing scientific rigour to research; biological and folklorm onemic are two examples of this genetic research. Consequently, scientific rigor gradually supplanted eugenics; in any case, ethics must always be present and not only when applying a certain research but also when questioning the aims of research.

Human beings –slow and uncontrollable breeders– have never been as advantageous for genetic research as, say, poultry, rodents, and fruit flies. Nevertheless, almost immediately after the rediscovery of Mendel's laws, in 1900, biologists began to apply them to the study of heredity in man –because he was man. In 1902, the British physicial Archibald Garrod convincingly showed that certain inborn errors of metabolism– notably alcaptonuria –were caused by a Mendelian recessive gene. In 1907, the Mendelian inheritance of human eye color was demonstrated in Britain by C.C. Hurst, a flower breeder. Clearly, early research in human genetics comprised the study of purely physical traits and diseases for their own sake However, through the first third of the twentieth century, human genetics was enormously influenced by eugenics –that is, by the cluster of ideas and activities centered on the aim of improving the quality of mankind through the manipulation of its biological heredity.

Invented as a self-conscious doctrine in the late nineteenth century, eugenics became a popular social movements after 1900, developing a large following in the United States, Britain, Germany, and many other countries. The backbone of the movement was formed of people drawn from the white middle and upper middle classes, especially professional groups. Its supporters included prominent laymen and scientists, particularly geneticists, for whom the science of human biological improvement offered an avenue to public standing and usefulness. Eugenicists declared themselves to be concerned with preventing social degeneration. They found signs of such degeneration in the social and behavioral discordances of urban industrial society –for example, crime, slums, and rampant disease; took these as symptoms of social pathologies; and attributed them primarly to biological causes– to "blood," to use the term of inheritable essence common at the turn of the century.

To eugenically-minded biologists, the causes of social degeneration had to be understood to be rooted out –which made the study of human heredity essential to the eugenic program. Such biologists understood eugenics to be the application of human genetic knowledge to social problems and the development of that knowledge to be the basic branch of eugenic "science". As a result, the human genetics program included the study of medical disorders –for example, diabetes and epilepsy- not only for their intrinsic interest but because of their social costs. A still more substantial part of the program consisted of the analysis of traits alleged to make for social burden-straits involving qualities of temperament and behavior that might lie at the bottom of, for example, alcoholism, prostitution, criminality, and poverty. A major object of scrutiny was mental deficiency –then commonly termed "feeblemindedness" which was often identified by intelligence tests and was widely interpreted to be at the root of many varieties of socially deleterious behavior.

A large fraction –perhaps most– of research in human heredity was pursued in laboratories established to develop eugenically useful knowledge.The most prominent of these institutions, both of which were ceated early in the century, were the Galton Laboratory for National Eugenics, at University College London, under the directorship of the statistcian and population biologist Karl Pearson; and the Eugenics Record Office of the Carnegie Institution of Washington's Department of Genetics, located at Cold Spring Harbor, on Long Island, New York, and headed by the biologist Charles B. Davenport. Eugenic science was institutionalized in Germany beginning in 1918, with the establishment ofwhat became the Kaiser Wilhelm Institute for Research in Psychiatry. The institutionalization continued with the creation, in 1923, of a chair for race hygiene at Munich, to which the biologist Fritz Lenz was appointed; and with the founding, in 1927, of the Kaiser Wilhelm Institute for Anthropology, Human Heredity, And Eugenics in Berlin, which was directed by the anthropologist Eugen Fischer, a conservative nationalist Catholic who then headed the Society for Radial Hygiene.

Staff at or affiliated with these laboratories gathered information bearing on human heredity by examining medical records of conducting extended family studies often relying upon field workers to construct trait pedigrees in selected populations –say, the residents of a rural community– on th basis of interviews and the examination of genealogical records. An important feature of German eugenic science was twin studies. By 1926, as a result of its various surveys and studies, the Eugenics Record Office had accumulated about 65,000 sheets of manuscript field reports, 30,000 sheets of special traits records, 8,500 family trait schedules, 1900 printed genealogies, town histories, and biographies.

Karl Pearson, an adamant anti-Mendelian, sought to determine heritabilities by calculating correlations among relatives or between generations for different diseases disorders, and traits. Studies emanating from his laboratories typically explored the relationship of physique to intelligence; the resemblance of first cousins; the effect of parental occupation upon children's welfare of the birthate; and the role of heredity in alcoholism, tuberculosis, anad defective sight. However, the approach that dominated eugenic science in most laboratories was not correlational but Mendelian analyses attempts to use phenotypical and family data to account for the inheritance of a variety of medical afflictions and social behaviors in genetic terms.

Typical of Mendelian work in eugenic science were the studies of Charles B. Davenport and his associates, which appeared in his comprehensive 1911 book, *Heredity in Relation to Eugenics* and in later publications. Wherever family pedigrees seemed to show a high incidence of a given character. Davenport concluded that the trait must be inheritable and attempted to fit the pattern of inheritance into a Mendelian frame. Although he noted that single

genes did not seem to determine important mental and behavioral characteristics, he did argue that patterns of inheritance were evident in insanity, epilepsy, alcoholism, "pauperism", and criminality. The mental and behavioral characteristics of different races were a mayor concern of Davenport's, who, like eugenic scientists elsewhere, held different national groups and "Hebrews" to represent biologically different races and express different racial traits. However, although he declared himself frequently on the subject, he actually did little research in it, particularly of a Mendelian type, except for an inquiry into "race-crossing" between blacks and whites in Jamaica, the effects of which, he concluded, were biologically and socially deleterious.

Davenport helped introduce Mendelism into the studies of "feeblemindedness" conducted by Henry H. Goddard, the psychologist who intoduced intelligence testing into the United States. Davenport provided field workers for Goddard's surveys of the mental characteristics of a local population in New Jersey and advice on genetic interpretation of the data.The surveys contributed essential material to two highly influential books by Goddard –*The Kallikak Family: A Study in the Heredity of Feeblemindedness* and *Feeble-mindedness: Its Causes and Consequences,* published respectively in 1912 and 1914. Goddard speculated that the feebleminded were a form of undeveloped humanity: "a vigorous animal organism of low intellect but strong physique –the wild man of today." He argued that they lacked "one or the other of the factors essential to a moral life an understanding of right and wrong, and the power of control", and that these weaknesses made them strongly susceptible to becoming criminals, paupers, and prostitutes.

Goddard was unsure whether mental deficiency resulted from the presence in the brain of something that inhibited normal development or from the absence of something that stimulated it. But whatever the cause, of one thing he had become virtually certain: it behaved like Mendelian character. Feeblemindedness was "a condition of mind or brain which is transmitted as regularly and surely as color of hair or eyes." According to later studies by Goddard and others, it also occurred with disproportionately high frequency among lower –income and minoritaty groups– notably recent immigrants in the United States from Eastern and Southern Europe.

Eugenic research in Germany before the Nazi period was similar to that in the United States and Britain, and much of it remained similar after Hitler came to power. The Institute for Anthropology, Human Heredity, and Eugenics, for example, continued to press investigations into subjects such as the genetics of diabetes, tuberculosis, and brain disease; the heritability of criminality; the effects of race crossing (with no particular emphasis on Jews or Aryans). However, during the Hitler years, Nazi bureaucrats provided eugenic research institutions with handsome support and

their research programs were expanded to complement the goals of Nazi biological policy, exploiting ongoing investigations into the inheritance of disease, intelligence, and behavior to advise the government on its sterilization policy. Fischer's Institute, the staff of which included the prominent geneticist Otmar von Verschuer, trained doctors for the SS in the intricacies of racial hygiene and analyzed data and specimens obtained in the concentration camps. Some of the material –for example, the internal organs of dead children and the skeletons of two murdered Jews– came from Josef Mengele, who had been a graduate student of Verschuer's and was his assistant at the Institute. In 1942, Verschuer succeeded Fischer as head of the Institute (and would serve postwar Germany as professor of human genetics at the University of Muenster).

Davenport, Lenz, and eugenic scientists in other countries managed, in the end, to expose genuinely Mendelian patterns in the inheritance of traits that could be well specified –color blindness, for example– and were entirely physical. Their works showed that single genes might account for such abnormalities as brachydactyly, polydactyly, and albinism, and for such diseases as hemophilia, otosclerosis, and Huntington's chorea. Lenz, in particular, also developed important mathematical methods for overcoming ascertainment bias –the tendency in human genetic field surveys to find a higher frequency for a given trait among siblings than its true probability of occurrence. Some fraction of their work thus contributed usefully to the early study of human genetics.

However, the fraction was rather small. Combining Mendelian theory with incautions speculation, they often neglected polygenic complexities in favor of single-gene explanations. They also paid far to tittle attention to cultural, economic, and other environmental influences in their accounts of mental abilities such as low scores on IQ tests and social behaviors such as prostitution. Some of Davenport's trait categories were ludicrous, particularly in studies on the inheritance of what he called "normadism", "shiftlessness", and "thalassophilia" –the love of the sea that he discerned in naval officers and concluded must be a sex-linked recessive trait because, like color blindness, it was almost always expressed in males.

Class and race prejudice were pervasive in eugenic science. In northern Europe and the United States, eugenics expressed standards of fitness and social value that were predominantly white, middle class, Protestant –and indentified with "Aryans". In the assumptive reasoning of eugenicists, lower-income groups were not poor because they had inadequate educational and economic opportunity but because their moral and educational capacities, rooted in their biology, were inadequate. When eugenicists celebrated Aryans they demonstrated nothing more than their own racial biases. Davenport, indulging in unsupportable anthropology,

found the Poles "independent and selfreliant though clannish"; the Italians tending to "crimes of personal violence"; and the Hebrews "intermediate between the slovenly Servians and the Greeks and the tidy Swedes, German, and Bohemians" and giving to "thieving" though rarely to "personal violence". He expected that the "great influx of blood from Southeastern Europe" would rapidly make the American population "darker in pigmentation, smaller in stature, more mercurial... more given to crimes of larceny, kidnapping, assault, murder, rape, and sex-immorality".

In the 1930s, in the United States and Britain at least, eugenic science –eugenically colored theories of human heredity– was increasingly criticized for its scientific shoddiness and social prejudice. It was charged with vagueness in identification of putatively heritable traits and with uncritical acceptance of hearsay evidence gathered in the field surveys. An assessment of the Eugenics Record Office pointed out, for example, that its vast body of records were worthless for the study of human genetics, not least because they fastened upon traits such as personality, character, sense of humor, self-respect, loyalty, holding a grudge, and the like, all of which could seldom be measured or honestly recorded if they were. Eugenic science was also indicted for its distortions of race and class bias and for its neglect of how social and cultural environment might shape socal behavior, not to mention performance on intelligence tests.

In the 1930s and 1940s, eugenics influenced the field of human genetics in the United States and Britain partly by making it unattractive to most of the new generation of geneticists. To be sure, the field was unappealing partly because the techniques and skills of plant and animal genetics, in which most geneticists were trained, did not readily transfer to the study of human heredity, which depended upon at least some medical knowledge as well as special mathematical methods. However, in the United States, where eugenic doctrine had been virulently deployed against minority groups, plant and animal geneticists were also discouraged from having anything to do with human genetics because of its associations with the racism, sterilizations, and scientific poppycock. One American geneticists recalled having been warned that it was just too difficult to get the necessary reliable information on human heredity. "The records are poor; classification is poor... Let's work with experimental organisms. The only thing you can do with human genetics is develop prejudices. And anyone who went into human genetics was immediately classified as a person of prejudice".

However, the eugenic idea remained tantalizing to some scientists and drew an exceptionally talented cadre into human genetics. The group included Ronald A. Fisher, J.B.S. Haldane, Lancelot Hogben, Julian Huzley, and Hermann J. Muller. One might call them "reform eugenicists" because, unlike their predecessors, they held that any eugenics must be free of racial and class bias

and must also be made consistent with what was known about the laws of heredity. In this latter regard, they had important allies among physicians like the British authority in mental deficiency Lionel Penrose, an anti-eugenicists, who thought that genetics might be advantageously deployed in preventive or therapeutic medicine. What bound Penrose together with reform eugenicists like Haldane was a deep-seated belief in the need to develop a sound science of human genetics.

Partly to emancipate the field from a prejudicial eugenics, the new students of human heredity preferred to search for well-defined, sharply segregating traits as immune as possible both to uncertainty in identification and to environmental influence. They thus welcomed with particular enthusiasm the rapidly increasing knowledge of the human blood groups, seven of wich were known by the early 1930s, which displayed patterns of inheritance that seemed to conform to Mendel's laws. The blook groups promised to open the door to the genetic mapping, via linkages, of the human chromosomes. Hogben, in his influential *Genetical Principles in Medicine and Social Science*, published in 1931, called attention to the recent development of mathematical methods for transforming data into tests of linkage, adding that if unambiguous markers like to blood groups could be found for every chromosome, then there would be a set of socially unbiased benchmarks in connection with which the human genome could be catalogued.

To Hogben and others, linkage studies were also promising for eugenic prognosis. Eugenicists had long been stymied by the problem of tagging the heterozygous carriers of genes for recessive traits, which were not expressed until –too late from a eugenic point of view– they joined homozygously in offspring. Linkage studies might reveal that a deleterious recessive gene occurred on the same chromosome as did one of the blood groups; anyone found to have that blood group would be spotlighted as a probable carrier of the recessive. Similarly, if the gene was a dominant, the identification of an infant's blood group would enable one to predict the probability –it would depend upon the degree of linkage– that the disease resulting from the dominant would be expressed in the child. Appropriate steps might then be taken to prevent the expression –or at least to mitigate the effects– of the disease itself. If the disease came on late in the child-bearing years, people fated to contract it could be adised before they had children of the chance of transmitting it to their offspring and they might then refrain from reproduction.

A good deal of effort was expended, especially in England, on the search for linkages, and also on surveys for consanguinity in the families of hospital patients suspected of suffering from recessive diseases. However, no linkages were found between, on the one side, the blood groups or any other universal, non-sex-linked character and, on the other, any type of genetic disease or disor-

der. Hogben's team was similarly unsuccessful, and so was every laboratory in the United States and Britain that attempted the task. Almost as disappointing was the search for consanguinity. Nevertheless, the research program of the thirties produced powerful mathematical methods of linkage analysis and, for the most part, a large amount of reliable data, particularly measures in Britain of the national incidence of consanguinity as well as of the incidence of numerous rare diseases. It was also advantageous, Haldane noted, to know that single recessive genes did not seem to account for goitre, pyloric stenosis, harelip, or spina bifida, among other maladies.

After World War II, biologists interested inhuman genetics sought to emancipate the field entirely from its eugenic associations and research ambitions. Lionel Penrose, appointed Galton Professor and head of the eugenics laboratory at University College London, managed to have his chair renamed the Galton Professorship of Human Genetics, the title of the laboratory's journal changed from *Annals of Eugenics* to *Annals of Human Genetics,* and focus its work on human and medical genetics as such, particularly on the study of hereditary phenomena that could be objectified quantitatively or otherwise. Penrose's most important ally was J.B.S. Haldane, the Weldon Professor of Biometry at University College, who, although still eugenically inclined, backed Penrose's scientific program, stressing in particular the essential importance to human genetics of biochemistry.

In the United States during the postwar years, a key figure in liberating human genetics from its eugenic attachments was James V. Neel, who had started out in fruit-fly genetics under Curt Stern, taken an M.D., and in 1948 assumed a joint faculty appointment in the Medical School and the Laboratory of Vertebrate Biology of the University of Michigan. Initiative for the creation of the post seems to have coe from the head of the laboratory, Lee R. Dice, a eugenically inclined ecologist who had persuaded the university to establish a small outpatient heredity clinic to help people learn whether they might have "bad" genes. Neel assumed responsibility for the clinic, and he spent part of his time exploring how the carriers of genetic disorders might be detected. However, he recalled, "When I came into human genetics, I had one, I guess absolute, guiding principle: Try to be as rigorous as I would have been had I remained with *Drosophila.* That meant picking problems carefully, problems where we could get solid scientific evidence about inheritance in man". Neel's search for solid scientific evidence –and for indicators of deleteriours genetic carriers– focused his attention on human blood. "You can spread it out, you can look at it, you can treat it objectively", he remarked, and by the late 1940s he had worked out the genetics of thalassemia and sickle-cell anemia.

During the 1950s and 1960s, human geneticists inb both the United States, Britain, and elsewhere advanced the objectification of

human genetics considerably through biochemical and chromosomal research, further removing the field from its eugenic past. However that past remains alive in memory and an awareness of it can assist us in thinking ethically about human genetics now and in the future.

In this connection, several points might be kept in mind. Eugenics was not an aberration, the commitment merely of a few oddballs and mean-spirited social theorists. It was embraced by leading biologists and it was integral to the research programs of prominent, powerful institutions devoted to the study of human heredity. The lure of alleged biological imperatives, having tantalized capable scientists in the past, could equally seduce them in the future, even though the expression of the imperatives may differ in language and sophistication. Indeed, eugenics remained a powerfully attractive idea even after the social prejudice of its early form was recognized and exposed. Objective, socially unprejudiced knowledge –the type sought by Haldane, Hogben, and their like-minded colleagues– is not *ipso facto* inconsistent with eugenic goals of some type. Such knowledge may, indeed, assist in seeking them. The enrichment of human genetics by molecular biology has in fact prompted some leading contemporary biologists to raise with enthusiasm the possibility of a "new eugenics" –a eugenics that, in the vein of the reform eugenic program of the 1930s, cold be free of social bias and, as a result of DNA engineering, could be scientifically achievable. The more that is learned in the future about human genetics, the more might it edge towards a reunion with eugenic goals –with all the hazards that such a reunion would entail.

Nevertheless, I doubt that a new eugenics will soon arise –at least not an overt eugenics. The social and ethical challenges of the Human Genome Initiative lie in the detailed issues on which this conference has focused, notably the use of genetic information in genetic counseling, diagnostic testing, insurance, and employment. The issues will turn on economic costs –who pays for what and how much– rather than on the quality of the gene pool as such. However, it is worth remembering that the pursuit of human genetic knowledge was intimately a part of the eugenics movement and that the results of this research –the claims of what human qualities, especially behavioral ones, were genetic– established part of what we deplore about the eugenics movement. And one hears echose of eugenic discourse in some of the claims –well-intentioned though they may be– by contemporary practitioners of behavioral genetics.

Many early eugenicists were scientifically and socially wellintentioned, too. Indeed, politically, a number were progressives or advocates of the socialist left. Goddard argued that, since certain anti-social deviates were feebleminded and that since their feeblemindedness resulted from their genes, they were not truly responsible for their behavior. He suggested that they should not

be imprisoned but should be placed in therapeutic institutions, where educations and training might make up for their genetic inadequacies. Yet however well-intentioned, their research yielded claims about the genetics of intellectual capacity and moral behavior that were stigmatizing to the so-called feelbeminded and members of various minority groups –and that were for the most part utterly wrong.

No doubt similar good intentions lie behind contemporary claims made about the genetics of behavior and mental disorder. However, there is reason to suspect that result concerning the genetics of, for example, alcoholism, manic depression, and the like may also be wrong and may also be socially stigmatizing as well as hurtful to families. The categories of behavior that one finds specified in some of this resarch are, in the vein of the early eugenic studies, of decidedly dubious merit. Declarations that a propensity for "traditionalism" is genetically based frankly call to mind Davenport's analysis of thalassophilia. The inferences about genetics drawn from these studies raise doubts in the mind of anyone familiar with the early eugenic literature. Just because genetic conclusions are couched in the language of RFLPs does not make the behavior categories about which the conclusions are reached any more reliable or persuasive.

Perhaps a code of ethics is needed for how genomic analyses of behavior should be handled. Perhaps, because of their stigmatizing potential, they should be published in a journal unabashedly entitled, "The Journal of Results that May Be Wrong". Perhaps they should not be announced in press conferences. More seriously, perhaps the genomic community should establish standards for how to deal with socially charged information. The greater the social explosiveness, the more rigorous should be the requirements of rigor and reliability for its publication. Whatever the case, the influence of eugenics on the history of human genetics suggests that it is not only how the results of research are applied that merits ethical scrutiny. It is also what questions are asked about human behavior, including racial and sexual differences –and how the results are handled.

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LESSONS FROM THE PAST: PROJECTS FOR THE FUTURE. THE HUMAN GENOME PROJECT AND THE SOCIAL CONTRACT: AN APPROACH OF LEGAL POLICY

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ABSTRACT

Science and law co-exist, although they are confronted in certain instances. The Human Genome Project wil give a unique character to each human being, and it is only logical to think of the implications to be derived from this fact, implications on which Law must give its opinion. This project must count upon international laws for the respect for law and professional ethics on the one hand, and for human rights on the other.

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Science and law co-exist, although they are confronted in certain instances. The Human Genome Project will give a unique character to each human being, and it is only logical to think of the implications to be derived from this fact, implications on which law must give its opinion. This project must count upon international laws for the respect for law and professional ethics on the one hand, and for human rights on the other.

How could the Human Genome Project and its applications in medicine benefits from the lessons of the past in matter of law? Is the influence of Law so powerful that it could have some influence upon the development of Science? Don't you believe it would be merely presumptuos to think we could draw from the Law some useful lessons which could be used to define what should be the Human Genome analysis?

The only lesson from the past I have in mind is Galilee's story. Thus I could conclude here this speech telling you that the best thing we could imagine for the Genome Project is that it should not become a matter of law with perhaps one exception about which I will tell you now a few words. In Galilee's story, Science and Law come into conflict because the concept of Science implied by the theory of Galilee and the concept of Law used by his opponents and judges opposed two worlds. Galilee's world was announcing a new period in human development in which Science will obey its own rules while the world of his judges was large ly based on religious principles which were supposed to apply to all human activities. As far as the Law in no more considered as a part of a global and unique view of how universe is conceived, the danger has disappeared. However, if the Law is not a way to enforce the idea we have about how our world should be, what should the Law do?

Let me imagine that the Law is useless and that the power of Science is sufficient enough to organize our life. But does Science say anything about justice, human rights or more simply about the way to divorce and to pay alimony to your wife?

We could then conclude that Science and Law, although they have their own autonomy, belong to the same world. In this world no one of them could dominate the other. Both are necessary to organize and even promote our every day life. Then, I come to my exception which I consider myself as the main role of the Law. The Law, I mean the legal approach, should not be regarded as an independant system of control and sanctions but as a realistic tool to maintain a close relationship between Science and Society, to make aware all those concerned by these two elements that the context in which Science is developing supposes a permanent interaction between Society and the scientific activities.

As far as we agree on this process, the problems are simple. Law does not intend to stop the development of sciences and we believe Science will not transform our world into a big laboratory. So the problematic is only to find a way in which Science and Law could operate all together. Unfortunately, this is where our difficulties begin.

As regard to the Human Genome analysis which aims to bring us a better knowledge of our genetic individuality, we have to con-

sider how far this project could affect our society, which evolution we could admit and which we should not.

For the first time in human history, the knowledge in genetics will enable science to completely identify and differentiate each human as genetically unique [1]. Will the possibility which are then opened to individual differentiation affect the Social Contract which govern Society? Will it reinforce the trend for more individual liberties? Or will it create a "brave new world" in which individual differences will be the basis of social inequality? In her address to the Fifth Economic Summit Conference held in 1988 in Roma, Prof. B.M. Knoppers expressed the view that the development of genetics implies the renegotiation of the Social Contract and suggested two founding principles: reciprocity which means exchange of information and mutuality which means civic responsibility [2].

I can neither assure you that the genetics technologies will lead to the renegotiation of the Social Contract nor that the Law could solve all the questions raised by the genetics technologies.

However, I would like to show that a legal approach is necessary to offer to our Society a way to deal democratically with the societal choices related to the use of Genetics.

The simple reference to the scientific means and the tremendous amount of money which will be devoted in the Human Genome analysis would have been sufficient enough to demonstrate "how big and how fast" public authorities and the community in general are concerned with Genome Projects [3].

But other reasons justify a public policy approach of this question: the fears and anxiety raised in the population by the biological revolution [4] but also the interrogations of scientists themselves about what they should do with the new biological power [5].

If we consider institutionnal issues are legal issues, the analysis of the role played by our democratic institutions in the Human Genome debate reveals a complete failure.

With the exception of the USA [6], Germany [7] and Sweden [7-1], no official assessment has been realized on the implications of the human genome analysis. Some countries addressed specific issues such as prenatal diagnosis, gene therapy or the use of DNA fingerprints. But neither the executive of the legislative branches which are supposed to represent the citizens did tackle with such a question.

The factual reason is probably that apart Japan [8] and the U.S.A.[9] no other country in Western Europe launched its own program in order to map and sequence the Human Genome. Countries are either associated in the Humane Genome Organization [10] or,

as member of the EEC, they are part in the European Community project on genome analysis [11].

The conceptual reason is that traditional public mechanisms have not till now been equal to the task of debating the questions raised by the new biology.

Governments which function often as leaders of many legislative initiatives have been very reluctant to address such issues. In France, for example, the Government asked for several reports in the field of bioethics [12] and even for a draft bill [13], but always refused to go further in the legislative process. In the United Kingdom, where the Government presented a bill on embryo research in Parliament [14], the proposed text left full choice to M.P's between the prohibition of research and its regulation.

Legislative bodies have not better succeeded in this way. So far as I know, there has been little significant legislative activity of a traditional sort on the subject of the new biology –that is, by a committee made up solely of members of the legislation considering a bill, through hearings and committee deliberation, leading to a debate on the floor of the legislature and eventually to the adoption of a status. A.M. Capron, who directed the U.S. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1979-1983), explained that "legislators want probably to stay at some distance from controversial issues in particular when a topic seems to implicate the issue of abortion. But they also realize that these issues require more sustained analysis than the legislative committee process would allow" [15]. Federal systems are also concerned with the specific problem to know at what level of government the question should be addressed. Judicial cases constitute another customary forum for law-making, especially in common law countries.

There has been some significant decisions by courts in the field of the new biology such as the New Jersey Supreme Court decision on surrogate motherhood in the Baby M case in 1988 [16].

As regard to genetics, courts have also dealt with cases in prenatal diagnosis [17] or the possibility to patent living organisms [18]. The disclosure to third parties (employers, insurance companies) of information obtained by genetic testing of adults is also an important matter for litigation [19].

Yet the courts are ill-suited to resolve all the questions in the context of existing law and the control of research experimentation can not be accomplished by courts without any specific legal references.

In matter of very difficult legal issues, case law does not also permit to know a priori what will be the legal solution adopted.

If existing institutional mechanisms have not yet been able to play their role in setting up a democratic debate in the field of genetics, who should do?

As other fields related to the new biology, genetics led to the development of new institutions.

Two categories of institutions are concerned.

The mandate for most of the groups in the first category is directly related to public policy and the law.

What solution should the government bring to a particular activity?

Some of these institutions have been mandated to give their own views on such an issue and to propose guidelines for a coming legislation.

This was the case in Germany with the Benda report on genome analysis [20].

Other groups are only requested to address the state of the art and to present the different alternatives offered to the legislator.

This is mainly the task of OTA in the United States with its major reports on Gene Therapy, Genetic Testing in Occupational Disease and Mapping our Genes [21]).

A second characteristic of the groups in this first category is autonomy.

Although they usually report to the government or to the legislator, these groups are independant from the existing administrative framework.

Sometimes, they are just ad hoc commissions outside the administration but relying on the administrative support of some ministries.

In other cases they are permanent autonomous institutitons already existing to help public authorities in defining new policies. The best examples is provided by the Law Reform commissions in several provinces of Canada and States in Australia [22]. It is also the case of the ethical Commission of the Medical Research Council in Canada, Australia, Nordic countries and in the United Kingdom [23].

Finally, new institutions have been created in some countries to deal specifically with bioethics issues. Such is the task in France of the Comité consultatif national d'ethique [24] or in the United States of the Congressional Biomedical Ethics Advisory Com-

mittee[25]. National committees also exist in Australia[26], Denmark[27], Italy[28], Luxembourg, Malta, Portugal [29] and Sweden. Spain is planning to have its own very soon.

The issue of membership is very important to look at the democratic aspects of these institutions. With the exception of the Law Reform Commissions, biomedical scientists and practitioners dominate the groups. This fact does not in itself seem a ground for criticizing a committee but it shows the limits of enlarging the bioethical debate to other professional groups.

However, lawyers, ethical and religious experts, as well as social scientists and members of the general public are often represented.

The second category of institutions concerned is formed by the increasing number of institutional review boards which are in the different countries in charge to review research protocols.

Of course, their major task is scientific review but they also contribute to the diffusion of ethics in research and practise.

The institutions, not all completely novel, that I have just described have played till now a major role in the development of bioethics. The work they have accomplished multidisciplinary, assessing and proposing bodies is great and their will probably extend their jurisdictions in the coming months to other areas covered by genetics [30].

However two lessons can probably be drawn from the present experience.

First, this is the importance of methodology in the legal approach of ethical issues.

Is the group empaneled to address a single issue or an ongoing set of issues? A group with a broad mandate has certainly the advantage to give a more coherent view on matter of law but a too broad mandate risks creating an ethics "bureaucracy".

Then comes the need for this new institutions to justify that the work accomplished, especially when it includes guidelines or draft legislation, takes into account the different opinions existing in the community. In order to satisfy with such an objective, specific methodology should be set up.

I will say that objective and impartial reporting is insufficient. Public opinion should not get the feeling that the new institutions are working on an insularity basis. Therefore a major effort to communicate should be done by institutions in carge with studying the legal and ethical questions raised by genetics.

Large symposiums should be organized to make the public aware of the importance and opportunity to deal with such issue [31]. Pre-reports should also be published and public hearings held in different localities.

The aim is not to built a false consensus but to create interaction between the proposals of the commission and the comments of the public.

The methodology adopted by Law Reform commissions in Australia and Canada constitutes a good example of what could be done.

The impact of the Human Genome analysis will probably impose the setting up of amplified and permanent means to fulfil with this task.

A second issue of great importance is to know how a further step could be accomplished in term of legislative process?

Except if all those groups come to the conclusion than there is absolutely no need for legislation, we have to think about this question: how should a decision be taken?

We observed that in many issues the executive and legislative branches have been reluctant to take the initiative of Law Reform.

Does it mean that the only possible reform is, as it was realized in Switzerland, to mention in the law that the principles elaborated by one of those new institutions should apply to the matter concerned? [32].

Couldn't we do an effort on this point and imagine an interactive approach that could contribute to promote a democratic process of decision?

Public votes are already used in societal issues. If it consists in letting a group of citizens drafting a bill and collecting signatures to submit this bill to a ballot such a procedure could be risky because it will exacerbate particular interests and controversial debate [33]. But if it obliges the government to propose its own bill or counter-project either to Parliament or to the vote of the citizens, it could sometimes stimulate in a good manner the process of law.

A popular initiative of Swiss citizens on reproductive medicine is under way to be transformed by the Swiss Federal Council in a governmental counter-project largely based on the proposals of the federal commission on reproductive medicine [34].

My remarks concerning the institutional approach would have not been complete without saying a few words about international cooperation.

It is obvious that scientific cooperation is a professional necessity from those involved in the ambituous program of genome analysis. The Human Genome Project has already been conceived on the basis of international cooperation [35]. Therefore, the question of international legal cooperation is already posed in two ways.

First we should consider how the ethical and legal guidelines which would apply to the coming common research realized on the ground of such a cooperation will be elaborated?

Who is going to do it? How could it be enforce? Could some national authorities prevent scientists in their juridictions to participate in the Human Genome Project? For example, you know that the European Commission has not yet accepted to participate in HUGO [36].

Secondly, what will be the appropriate international forum for legal cooperation?

The Council of Europe has since many years adopted a methodology and a program in bioethics and genetics but it is only a regional organization [37]. On the International level, who has no international program of cooperation except the publication of national legislations.

So, do we need a specific organization linked to HUGO as we now have an international ethics committee on AIDS or is it possible, as the Secretary General of the Council of Europe suggested, to develop an international cooperation from a regional one [38].

Unesco which since 1990 has established a two year program on Science and Ethics could also bring its contribution to the relationship between Science, Ethics and Culture [39].

I know that many of the international projects concerning the Human Genome analysis such as HUGO or the EEC program have now substantial money to fund ethical and legal studies.

I have no idea of what was the mind of those who decided to include this legal studies in their programs but I guess that they merely wanted to prove that these programs will be realized in respect with the law and professional ethics.

However, this proportion of legal and ethical work will appear quite illusory if, prior to any study, some principles are not internationally recognized to be used as references. Among these principles comes first the respect of the rights of individuals such as informed consent, confidentiality and access to genetic data. But equitable diffusion of genetic information for scientific and therapeutic purposes, prohibition of any military use of genetic information as well as the prohibition of compulsory state policy

which could affect the individual genetic inheritage should also be considered.

Therefore, legal and ethical studies at the international level should also be coordinated to facilitate the assessment of international programs and appropriate decisions.

It is then rather difficult to reach to any other conclusion than the following!

Mapping and sequencing the Human Genome supposes first mapping and sequencing the legal approach to the Human Genome Project.

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22. See the working document issued by the Law Reform Commission of Canada on biomedical research (1989), that 1985 Ontario Law Reform Commission report on reproductive technologies and the numerous reports published by the New South Wales Law Reform Commission (organ transplants, Artificial Insemination, IVF, surrogate motherhood).

23. In Canada, the Medical Research Council played an important role in the elaboration of guidelines concerning research on human beings; in Australia, the first national guidelines concerning reproductive technologies were elaborated by the National Health and Medical Research Council Ethics Committee.

24. Presidential decree of Feb. 23, 1983 instauring the Comité consultatif national d'éthique pour le sciences de la vie et de la santé.

25. Established by statute (P.L. 99-158), the Biomedical Ethics Advisory Committee is composed of 14 members distinguished in fields relating to biomedical ethics.

26. **The National Bioethics Consultative Committee** has been set up in 1989 by the Federal Government.

27. **The Danish Council of Ethics** has been established by law n.° 353 of June 3, 1987.

28. **The Italian Committee** has been set up in March 1990 and consists in 40 members.

29. **The Portuguese committee** created in June 1990 is very similar to the French Committee.

30. For a comparative overview of National Ethics Committees, see **Byk, C.** *Les instances d'étique en droit comparé* in Cahiers Internationaux de Sociologie, Vol. LXXXVIII, 1990, p. 215.

31. See The International Symposium titled "Procreation Genetics and the Law" organised by the French Government in January 1985, proceedings published by Actes Sud, 1985.

32. See Article 13 of the Legge sanitaria of April 18, 1989 of the canton of Ticino which explicitly says that physicians have to apply the guidelines on reproductive medicine of the Swiss Academy of Medical Sciences.

33. See the 1988 Californian ballot initiative to legalize voluntary euthanasia. The initiative has in fact failed because the required number of signatures has not been collected.

34. The initial project concerned the amendment of article 121 of the federal constitution to prohibit the potential abuses of reproductive technologies and genetic engineering; see also the report of the Commission d'experts pour la génétique humaine et la médecine de la reproduction, Berne, 1988.

35. The initial project which goes under the name HUGO (Human Genome Organization) was initiated by some 32 scientists from the participating countries.

36. This is largely due to the action of European MP's who have critized on ethics grounds the proposed program of the Commission on predictive medicine. The adopted proposal which has been renamed genome analysis will last two years instead of a previous three years period.

37. The Parliamentary Assembly adopted several resolutions on genetics and embryo research (1982, 1986, 1989) while the Committee of experts on Bioethics (CAHBI) prepared since 1983 harmonized guidelines in the different fields covered by bioethics.

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DIAGNOSTIC PROOF AND GENETIC TESTING

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ABSTRACT

Genetic testing and diagnostic proof pose ethical and legislative problems. The development and carrying out of tests such as the detection of phenylketonuria in new-born infants or the detection of Tay-Sachs disease have shown the need for norms of application. The same may be said with regard to genetic therapy. It is obvious that biomedicine is advancing rapidly and that the scientific aspects on the one hand and the ethical ones on the other, relative to the same research project, are not considered by the same people. This fact shows the need to revise the personal perspectives of experts in ethics and of legislators, to the extent that scientific-technical advances with social implications are made.

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Genetic testing and diagnostic proof pose ethical and legislative problems. The development and carrying out of tests such as the detection of phenylketonuria in new-born infants or the detection of Tay-Sachs disease have shown the need for norms of application. The same may be said with regard to genetic therapy. It is obvious that biomedicine is advancing rapidly and that the scientific aspects on the one hand and the ethical ones on the other, relative to the same research project, are not considered by the same people. This fact shows the need to reduce the personal perspectives of experts in ethics and of legislators, to the extent that scientific-technical advances with social implications are made.

At a meeting devoted to the future of a field as dynamic and scientifically exciting as molecular genetics –a future tied today to the modern mantra, "mapping the Human Genome"– it is perhaps not surprising (albeit somewhat disappointing) that only on the last day does our attention turn to history, to draw "lessons from the past". Some of those lessons, as we have already heard, are dramatic, indeed horrifying. It would, for example, be difficult (and very wrong) to overlook the role that a perverted genetics played in the Nazi policy of "racial hygiene". Nor can we ignore the lingering effects of this eugenic heritage on clinical genetics in the post-War era.

The Seeming Innocence of Screening and Testing

In linking these "lessons from the past" to "prospects for the future", as the title for this session does, I am sure that the meeting's organizers did not intend to imply that we are bound to repeat the past, much less that learning from the past means emulating it. Yet I suspect that were it possible to put aside the history of eugenics discussed by Professors Müller-Hill and Kevles, the topic of my talk –"Testing and Screening"– would be less likely to raise concerns about the dangers of emulating the past. That is, despite the attention and concern that has focused on certain aspects of human genetics, such as genome mapping and gene therapy, genetic testing and screening today provokes little excitement.

Nevertheless, I will try to show that screening and testing should be topics of central concern to anyone considering the ethical issues raised by modern genetics. Furthermore, experiences with testing and screening have a great deal to teach us about the potential uses (and *misuses*) of the knowledge garnered through mapping the Human Genome and about the potential for public enthusiasm to outrun medical knowledge.

The Focus of the Paper

While science is universal, ethics and public policy are very provincial. For better or worse, this insularity (or, less pejoratively, this particularity) is an inevitable aspect of my presentation, which describes the development of screening and testing in the United States, looking back to newborn screening and pre-

natal testing, and then forward to susceptibility and carrier screening.

The rapid increase in the number and technical capacity of screening methods for inherited conditions that can be expected over the next decade will affect many relationships. Plainly, some specific legal responses to this increase in genetic capabilities are possible, such as the passage of legislation to protect the confidentiality of genetic information and to prevent discrimination against those who have –or who are believed to be at high risk of developing- a genetic disability.

Yet such responses, valuable as they may be, only address symptoms and do not respond to the underlying problems that the genetic techniques uncover. If we are to address the fundamental issues, we need to elevate them to a level of much greater public visibility, for if deeper problems are going to be overcome, some collective redefinitions in concepts and standards will be required.

The history of screening and testing

Before we can look to these basic issues and attempt to understand their implications for the future, we have to look back to experiences with genetic screening and testing. These two terms are sometimes used interchangeably while other times they are used, as I do here, to refer to separate though related activities. When the difference is drawn, screening connotes the initial action and testing encompasses diagnostic follow-up.

Screening may be undertaken for several reasons. In the words of a National Research Council study:

> Genetic screening may be defined as a search in a population of persons possessing certain genotypes that 1) are already associated with disease or predispose to disease, 2) may lead to disease in their descendants, or 3) produce other variations not known to be associated with disease [1].

The three types of screening –medical management, reproductive and research– mentioned in this definition can be further differentiated in a number of other ways. For example, one might focus on whether the screening method is well validated or is still experimental, or whether it involves a biochemical test for a gene product, a direct enzyme assay, or an analysis of variations in DNA base-pairs within in a kindred. Based upon the results of a *screen,* further diagnostic testing may then be under-

taken to confirm or rule out the existence of the genetic condition in question.

Screening for Treatment: The PKU Story

The earliest mass genetic screening program in the United States is now almost three decades old: newborn screening for PKU (phenylketonruia). Looking back at this program –which is so routine today that it hardly ever excites any professional much less public attention– reveals a history that may be very infomative for those engaged in genome research today. As we will see, the lessons concerns scientific naïvete, medical mistakes, public overconfidence, premature action, and a willingness to use coercion to achive collective goals. Furthermore, it may be that some of the concepts absorbed from screening for inborn errors of metabolism (such as PKU) are misleading as we move into an era when genetic screening may aim at conditions that are at once more complex and less obvious than the single-gene defects that have been the major focus of medical genetics until now.

In PKU, defects in the metabolic process in which phenylalanine is catalyzed to tyrosine creates an amino acid imbalance that produces harmful changes in the central nervous system. It had been known since the 1930s that an elevated level of phenylalanine is associated with mental retardation [2]. And by the mid-1950s it had been shown that lowering dietary phenylalanine could reverse PKU's major biochemical abnormalities. Yet by the time the condition is clinically detectable, it is too late to institute dietary treatment because severe and irreversible mental damage has already occurred.

Thus, effective treatment of PKU became possible only when, in 1961, Dr. Robert Guthrie developed a bacterial inhibition assay that could be applied to tiny blood specimens collected on filter paper from a heel prick of new babies right before discharge from the hispital. Field testing of the Guthrie method began in 1962 and showed that when the test was used with infants who had had adequate exposure to proteins, the blood screening method let few false negatives slip by. In order to avoid missing cases, the presumptive level of serum phenylalanine was set fairly low, which produces a high rate of false positives (over 90%). Thus, diagnosis depends upon follow-up testing, ideally during the first month of life. Children found to have PKU can then be placed on a commercially available diet that has a very low level of phenylalanine (while also supplying other essential

 amino acids); it is recommended that they remain on the diet into late childhood.

Although at the time, the inicial trials of the Guthrie assay left many questions unanswered –both about the testing methods and about the disease itself– the prospect that a cause of retardation could be eliminated soon generated enthusiasm among the national and state mental retardation associations for routine screening of all newborns. In Massachusetts, the state healt department promoted a large-scale trial (with the state lab being responsible for running the assays on the serum specimens) that was successful in screening most infants. This trial program operated without legal compulsion, yet in 1963 the state became the first to adopt a mandatory genetic screening statute –spurred by the health department director (who also chaired the public health services committee of what is now known as NARC, the National Association for Retarded Citizens).

At the time, the NARC committee merely urged states to adopt laws directing each state health board "to make recommendations for appropriate screening tests as they are developed and accepted". The following October, however, NARC adopted the committee's conclusion that states be recommended to adopt laws requiring PKU screening for all newborns. By the end of 1965, a majority of states in the USA had such laws. Althogh a few have since repealed them, 45 states still have mandatory statutes.

The adoption of such laws seems puzzling, not the least because the voluntary programs seemed to have been reaching most infants. Moreover, the rush to legislate occurred well before answers were available to several important biomedical questions, as the Nationl Research Council committee observed a decade later. In particular, the significance of elevated phenylalanine was not well understood at the time, nor had the variations from "classical PKU" been differentiated. For example, the fact that some degree of hyperphenylalanemia does not necessarily cause retardation was not fully established; yet this meant that a large number of the children placed on a low phenylalanine diet were not at risk for retardation in the first place, which confounded interpretation of the studies that aimed to determine whether adopting the diet could ensure normal intelligence in children with PKU.

Likewise, the adoption of widespread screening occurred before sufficient time had elapsed even to measure the regime's impact on intelligence, which requires the testing of capacities that are not reliably measaured until later in childhood. And the proper

level of phenylalanine –to avoid the detrimental effects of *too little* of this essential amino acid (as well as inadequate tyrosine)– had not been worked out, nor had physicians decided when it was safe for children to go off the special diet (age 2, 6, 10, or never?).

The history of screening for PKU in the USA (which has been followed in a number of states by the addition to the screening statutes of other rare inborn errors of metabolism such as Maple Syrup Urine disease) is interesting but the details are less important for our present discussion than the implications of the whole experience for potential uses of the data now being produced by the genomic cartographers. Before we further explore those implications for gene mapping, we should look briefly at another area of "testing and screening", namely experiences with reproductive screening.

Screening for Reproductive Purposes: Tay-Sachs and Sickle Cell

Given the way the public and its elected representatives were convinced to support mandatory PKU screening –that is, as a means of preventing mental retardation– it seems hardly surprising that the programs were generally not perceived as "genetic" at all. Instead, in the USA the public's recognition of the potential impact of truly genetic testing came a decade later with the commencement of a number of efforts to screen carriers of autosomal recessive disorders. Such screening produces information that typically has no necessary implication for the health of the person screened but that indicates a risk (usually 25% in each pregnancy) for offspring if one's mate also carries the same (or a similar) abnormal gene.

Screening for two diseases in the early to mid-1970s provide illustrative examples, both involving diseases that occur at a much higher than average rate in a minority population in the United States. The first is largely a success story: beginning in the Baltimore-Washington area in the early 1970s, community based screening programs for Tay-Sachs disease (a progressive neurological disorder that is typically fatal between the second and fifth year of life) were offered to Jews of Eastern European extraction. Success is measured not in the large percentage of the at-risk population of child-bearing age who participated but rather in such facts as: 1) a good educational effort, resulting in only a small percentage of the nonparticipants having not heard of the program, 2) enrollment having been based on informed, voluntary consent of adults (most programs would not test

children), and 3) confidentiality of test result having been maintained.[3]

Several factors were probably crucial to the success of those programs that worked. First, the programs were mounted by university researchers who –having no propietary interest in the testing– were willing, indeed eager, to have the ethical design of their programs widely discussed both among colleagues and consultants and with the communities affected. Second, the programs were aimed at a community with a sense of self-identity and institutions (synagogues and community centers) where information about Tay-Sachs and the screening program could be spread and participation could be endorsed by respected leaders. Third, the members of these communities were usually well educated and sophisticated users of the health care system. Fourth, most children born in these communities result from marital unions, so that both partners have a stake in knowing whether they were carriers and making reproductive decisions in light of that knowledge. Fifth, and perhaps most important, Tay-Sachs offered something of real utility because it was linked with the ability to perform a prenatal test for any pregnancy that resulted from the union of two carriers; if the results showed the fetus to be homozygous for the Tay-Sachs gene, the parents could choose to terminate the pregnancy and to conceive again, with 3:1 odds favoring the next fetus not being affected. Although selective abortion understandably excites concerns about genocide among many ethnic and racial minorities, in the context of a severe autosomal recessive condition, the results of screening and prenatal diagnosis actually *improve* reproductive prospects within families in which the disease had previously occurred. When a disease is devastating enough, many pregnant women will abort rather than run the risk (even if only 25%) of bearing (another) affected child.

Despite the predicates of success, not all community-based Tay-Sachs programs achieved a high rate of screening; the program in Montreal was one such example. And when higher rates opf screening were obtain, questions sometimes arose about their ethicality. As Holtzman observes, the more than seven-fold increase in the rate of screening in the Montreal Jewish when a program was introduced into the high schools may well be attributed not only to the greater ease of obtaining specimens in that setting but also to external pressure[4].

The risks of coercion and of adverse consequences to persons screened can be seen even more starkly in the experience in the USA with screening in African-American communities for sickle cell anemia carriers, which also began in the early 1970s. At this

time, no means of prenatal diagnosis existed, so that carrier-carrier couples were faced with the choice of not reproducing or of doing so with the knowledge of a 25% risk. A person identified as a carrier might even not want prospective mates to know this information, for fear of being ostracized. Furthermore, some employers and insurers, acting from ignorance or malice, treated heterozygotes for the sickle cell gene as though they had the disease and attempted to place limits on, or even to exclude, them. Before these problems with sickle cell carrier screening were perceived, screening programs were launched by community groups, minority politicians supported governmental funding (sometimes merely as a means to get their constituents access to *some* portion of governmental health funds and to draw the attention of researchers to the disease), and seventeen states passed laws mandating screening in a variety of settings, from schools to marriage license bureaus to custodial institutions. With greater clarity about the program's problems and the misuse of results, Congress adopted the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs and Genetic Diseases Act of 1976 under which programs supported with federal funds have to be "wholly voluntary" [5].

Commenting on this episode, physician-lawyer Philip Reilley has pointed to the "glaring errors, including egregious drafting mistakes that hopelessly muddled the scientific facts about sickle cell anemia" as demonstrating "the abyss that separates lawmakers from thechnical experts"[6]. Like the PKU experience, the experience with sickle-cell screening also sounds a cautionary note as we contemplate the uses that my be made of the results of genome mapping, namely the risk that programs will move too quickly to *de facto* and even *de jure* compulsion, while ignoring the risks of discrimination and the potential difference in diagnosing "in-born" as opposed to "acquired" diseases or disorders.

What lies ahead for genome mapping?

I hope that what I have said so far demonstrates two things: first, that even a topic as unglamorous and as apparently without noncontroversy as genetic screening and testing actually raises many genuine ethical and public policy issues, and second, that gene mappers would do well to learn from our experience with screening and testing. Lessons can also be garnered from other areas of the new genetics which are thought of as more controversial, like gene therapy. Since other speakers have not pointed to these lessons, I will describe them briefly.

First, I want to emphasize the risk that we in ethics and policy face of addressing the wrong issue, often because scientists themselves mispredict the future. Let me illustrate this with an example drawn not from genetic screening but from gene therapy (another area on which the genome project will have great impact.)

In the 1970s and early '80s, the general expectation was that the first attempts at gene therapy would be for the hemoglobinopathies. As it turned out, that expectation was both right and wrong. It was right in that the first attempt to use recombinant technology in gene therapy was Kline's unauthorized and unsuccessful attempt to treat several thalassemia patients. But it was wrong because the reason others did not perform or support such experiments was that modification of hemoglobin function turned out to require a level of genetic regulation that gene therapy techniques are still not able to achieve. So the target diseases became those –like ADA deficiency– where such regulation of the inserted genetic message does not seem to be necessary for therapeutic efficacy.

This change in technique was not necessarily of ethical import. Likewise, a further change from expectations –the switch from attempting to modify hematopoietic stem cells to modifying circulating lymphocytes– was not in itself ethically significant. But the further change ofattempting to treat a genetic disease to treating cancer with genetically modified cells does seem to me significant for ethical and legal analysis. The first experiment with human subjects involving gene transfer approved by the RAC (Recombinant DNA Advisory Committee) at NIH involved the use of tumor-infiltrating lymphocytes (so-called TIL cells), tagged with a genetic marker through gene transfer, in treatment of malignant melanoma. The second experiment, approved just this fall, involves inserting and active gene for tumor necrosis factor into the TIL cells. These approvals were given before the first attempt to use gene therapy for a genetic disease, namely ADA deficiency. As French Anderson notes in an editorial in the latest issue of *Human Gene Therapy*, besides treating cancer, gene therapy may also prove useful in treating cardiovascular disease (both as an aid to healing after surgery and by decreasing artherosclerosis through increasing LDL receptors), infectious diseases like AIDS, and as a "sophisticated drug delivery system" applicable in general to all diseases. [7]

I point to this history to draw two very basic and perhaps obvious lessons: first, that biomedical science develops in unpredictable ways, and second, that when those developments depart sufficiently from what biomedical scientists have predicted, ethicists and policymakers must also reevaluate their perspective and perhaps rewrite their prescriptions. In the case of gene therapy, the shift from the hemoglobinopathies to ADA-deficiency and even the shift from the "permanent" changes expected from stem-cell alterations to the temporary ones created by recombinant lymphocytes may not have been ethically significant, but the shift from treating genetic diseases to being merely a means for targeted drug delivery seems to me to call for ethical and legal reexamination. At the very least, it should make us ask again a basic question: not just "What is disease?" but more particularly "What is a *genetic* disease?".

Normality and Abnormality: Open for a New Look?

The need to reexamine our ideas about genetic disease is likely to arise not only from gene therapy research but also very urgently from the results of the Genome Mapping Project. For example, what consequence will there be for concepts of "normal" and "abnormal" when molecular genetics demonstrates that the line of difference between the "disease" and "nondisease" is nothing more than the rearrangement of a single DNA base-pair (out of the billions in every cell).

Questions like this can seem very philosophical (in the perhaps pejorative sense of being merely of intellectual interest), but I am convinced that they can have profound practical implications as well. In terms of my assigned topic of "testing and screening", consider what happens when a test shows an individual to be "abnormal". Certainly, part of the result is to separate that person from others, to generate the sense of the person being very different. To the exent that the difference is understood to be as minor as a single DNA base-pair –and hence perceived as basically random, the sort of chance event that could easaily happen to anyone, rather than as the more major change that marks a person as "diseased"– then the perception of distance between affected and unaffected persons may disminish. [8] This would have obvious (and beneficial) implications regarding a major concern arising from genome mapping, namely, the risk that the ability to detect more genetic differences will create more instances of discrimination against those marked as "abnormal".

Two areas in which the issue of discrimination are frequently cited are employment and insurance (especially in countries, such as the USA, in which work and insurance are tied to a competitive market place rather than being derived as a matter of social entitlement). The potential that information derived from genome mapping will greatly enhance the ability of genetic testing to "sort" people into different groups based on genetic differences raises an interesting challenge. It is usual to reflect that challenge back onto the genetic enterprise itself: to say, in other words, that the genome project creates a risk that "genetic predictions" (i.e., predictiions about the future occurrence of illness in an individual who carries a gene associated with greater than average susceptibility to a particular illness) will be used by employers and insurers as screening devices. This way of viewing the challenge is legitimate but I would like to turn the challenge around and ask instead: what are the implications of any new genetic predictive capabilities for our notions of insurance and employment? For example, in the field of health insurance in the USA, we have seen a movement from a risk-sharing model to a group-narrowing model –in other words, fom seeing ourselves as all being in roughly the same situation (thereby making it morally desirable to spread risks as broadly as possible) to seeking our individual advantage in placing ourselves in a group from which we have excluded people who are at higher risk than ourselves. When the exclusions are based on voluntarily acquired risks (such as from smoking), they have gained general public support. Such exclusions do not seem ethically objectionable, so long as we apply a fairly strict understanding of the term "voluntary". But exclusions grounded in genetic differences are less benign.

Nonetheless, it would be a mistake to conclude that genetic testing has no place in insurance. Whether it is acceptable depends not on abstract ethical principles but on our conception of the purpose of insurance.

Thus, the outcome of the Genome Project could be to force us to reevaluate the principles underlying insurance. Likewise for employment, wheter we regard everyone as entitled to compete for any job or belive that limits can be placed based on the costs (of illness, etc.) when a particular person works in a setting that exposes him or her to risks to which the person in unusually susceptible. Does "voluntary assumption of risk" resolve the problem or are there other desiderata regarding employment that may override individual willingness to assume a health risk? If a person is excluded from a workplace, what guarantees of comparable work must be available? Does it make a difference if the ge-

netic susceptibility is linked with a particular ethnic or racial group –so that a policy of exclusion might remove an entire racial or ethnic group from a particular type of employment? What if the potentially dangerous condition (such as toxic fumes) only affects a small number of people rather than affecting all people and simply harming those with peculiar susceptibility more rapidly or more severely? Such questions involve a reevaluation of the employee-workplace relationship generally; they are provoked by the potential use of genome mapping results in genetic testing programs but they are questions of broader interest than just to people concerned about genome mapping policies.

Mandatoriness

I have already argued that the history of genetic testing and screening shows the risk that they will be made mandatory innappropriately or at the least prematurely. I also mentioned in passing that there was quite a backlash against such developments and a renewed emphasis on the requirements of voluntariness. The genome mappers may provoke a challenge here as well –indeed, I believe that they already have. For example, in light of the importance of linkage analysis to mapping and diagnosis, we may need to rethink the concepts by which we describe our relationships and duties. In light of the genetic connections that bind people to one another, in terms not only of inheritance but also of molecular diagnostics, what are the proper meanings of "autonomy" and "privacy"? Don't I have some obligation to allow myself to be tested if that is the only (or by far the best or easiest?) way to map a gene that is of potential importance to the health of other members of my family? What if the knowledge has no immediate potential to benefit my family but is scientifically important? Or might aid in the detection of disease in other families sometime in the future?

Even more difficult questions will arise as genetic screening and testing gain the ability to predict more and more conditions (including those that would not today be labeled a "disease") in the fetus. It is too son to predict what consequences might all this have for our predisposition to protect free choice in private matters generally and in medical care in particular. But it is clear that more than a reexamination of voluntariness and mandatoriness will be needed: along the way, we will need to examine what we mean by such concepts as "responsible parenthood". Such a notion already exists in the context of behavior toward *born* children and may be extended to reproductive choices as well –indeed, this can already be seen in a number of unfortunate judicial decisions upholding forced cesearen sections. In light of such

cases, the intrusions inherent in involuntary genetic testing could actually be regarded as less onerous, particularly if those doing the tests did not plan to force an intervention afterwards but planned to rely on the person's conscience (and other pressures) to coerce "responsible" behavior once the results of the genetic test were known.

Conclusions

In this essay I have attempted to do several things: to sketch the history of genetic testing and screening and draw implications for genome mapping, and to speculate about a broad range of consequences in the testing-screening arena as the findings of the mapping project begin to be applied. Let me close, then, by summarizing a few of the basic lessons that we might draw from our experiences thus far with genetics in the public arena.

First, not only lay society but the health professions have been ill-prepared for new genetic knowledge and technologies. As a result, health professionals often have not played an effective role either witch individual patients or in the process by wich public policy was formulated. Further, we have seen that genetic technologies may be put into use in nonhealth-care settings by people who have little connection with science or medicine.

Second, although we tend today to regard the public as fearful of genetic developments, history also shows that the enthusiasm of the public (or at least of its elected representatives) for a new technology may rapidly outstrip knowledge of how to use it wisely. Programs have even be adopted that relate to genetic diseases without any real appreciation of what difference, if any, attaches to the disease of interest being "genetic". Instead, the program may be justified to policymakers on economic or other grounds.

Third, despite ritual affirmation of the value of personal self-determination, it would be naïve to think that when policymakers become convinced of the value of genetic screening or testing they will refrain from mandatory measures, especially if the health of children appears to be involved. Furthermore, if services do become routine, then failure to use them may open a person to accusations of behaving irresponsibly. "Responsible" behavior may also be encouraged by the economic incentives offered by employers and insurers, not solely through mandatory legislation.

Finally, history shows us the ways in which the exceptional becomes the routine. And when something becomes routine, incremental changes may occur in our moral attitudes, whether it

is about our mutual obligations to one another (can I exclude you from my insurance base because you're at risk of getting sick?), about who qualifies as a member of the moral community (are the unborn included?), or about parents' rights to make choices about their children's health care (does that extend to newborn tests for in-born metabolic problems?). Not all changes are bad, and many are beyond the ability of anyone to prevent, especially when they arise from new knowledge which is there whether one likes it or not. But we ought still try to anticipate the probable or even possible consequences of the genome mapping project and to avoid harmful ones if we can, a prospect that is improved if we will learn from our experiences this far with genetic testing and screening.

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   The number of states using federal funds under the block grant to support mandatory newborn screening programs exceeds the number of states offering screening on a voluntary basis.
   Holtzman at p. 223.

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8. If such a change in perception occurred, it would likely then extend to other genetic differences of a more major sort, as for example, the rearrangement or deletion of large pieces of a chromosome.

CLOSING SESSION

CLOSING
SESSION

CLOSING REMARKS

Santiago Grisolía

Institute of Cytological Research, Valencia (Spain).

CLOSING REMARKS

Santiago Grisolía

Institute of Cytological Research, Valencia (Spain).

Your Majesty,

In the name of the distinguised group of personalities from the basic, medical and social sciences, etc., who have taken part in this workshop, and on my own behalf, I should like to thank you for your generosity and for honouring this Congress with your presence today.

Your presence clearly shows the deep concern of the Crown for science and its effects on society. I should also like to mention the support and protection Your Majesty has given for many years to those less fortunate ones who suffer physical and psychic disabilities.

It is therefore quite logical and fitting that Your Majesty should take part in and preside the Closing Session of this II Workshop on International Cooperation for the Human Genome Project, wich has been devoted to the ethics of the matter. In this workshop, problems have been discussed that may affect new groups alienated on account of genetic causes with regard to employment, identification, insurance, etc.

We are on the threshold of a huge transformation in society that will to a great extent be due to the rapid pace of development and progress in scientific knowledge. As His Royal Highness, the Prince of Asturias quite rightly said a few weeks ago in Valencia "the development of a country depends more on its creative capacity than on its natural resources".

We may perhaps not realize what a powerful factor for the development of a nation scientific growth means, or the social changes it implies, obviously, genetics is today unrivalled among the sciences in this respect. Genetics is now about to take a gigantic step forward: to attempt to know the Human Genome, which has been compared to the Apollo Project on account of its dimensions and novelty. Yet I believe it is even more than this, for this project does not end with the drawing out of a map that locates each and every one of the 50.000 to 100.000 genes that represent the Human Genome, nor with the identification of each one of its components.

Apart from the immediate advantages that this entails for medicine and the new technology it brings, to possess the "dictionary" will enable us in future years –perhaps in the new century– to come to know ourselves better.

Like all advances, the Human Genome Project gives rise to new problems. In this sense, this is why this Congress is historically important, for participants in same have shown, from an interdisciplinary approach, their concern and fulfilment as members of the scientific community by publicly and clearly discussing the ethical problems posed and to be posed by the new knowledge.

When i was working at the University of Chicago in the building next to Stagg Field, I can remember the photographs taken of the occasion of the first chain reaction carried out on December the 2nd, 1942. In these photographs, everybody was smiling; however, the chain reaction finally killed 40,000 people in Nagaski alone. Thus, scientists do not wish the same thing to happen now as happened to those who took part in the development of the atomic bomb. These scientists later regretted not only their participation, but also the iron censorship that prevented any clear discussion of the possible ethical implications of their research.

From the social point of view, the dilemma is obvious; to protect both the individual and society, too. To this end, clear discussion is required and one cannot wait until their is suitable legislation. For example, in th United States there is the so-called "Human Genome Privacy Act" –although it is currently being postponed– which is a draft of a law with the aim of giving the individual the right to disclose of otherwise his or her genetic identification. Thus discrimination as to employment, insurance and education will be forbidden, for it seems there have already been cases of discrimination on grounds of genetic evidence. It is thought that similar laws will be suggested in other countries. But jurists and politicians need time to think and act. It is therefore an urgent need for the scientists themselves to act through private means such as foundations which, even though they have not the economic capacity of state entities, do have the agility that official organisms lack and cannot have. For this reason, I should like to publicly mention and thank the generosity of the BBV Foundation, which has begun its activities with a meeting as important as this, a meeting of such vast universal projection as the II Workshop on International Cooperation for the Human Genome Project: Ethics".

Finally, I should like to thank all participants who have made this meeting possible, and particularly Her Majesty the Queen for her special sensitivity to these problems.

Luis Oro

General Secretary to the National Planof the I + D.
Interministerial Committee for Science and Technology

On behalf of the Interministerial Committee for Science and Technology, I should like to express my thanks for the invitation to take part in this act, in which we have had the occasion to listen to important conclusions on the Human Genome Project, a project that is inserted within the growing framework of scientific internationalization, and has the oustanding merit of posing its possible repercussions at the same time as work is being carried out on it.

The Interministerial Committee for Science and Technology, in which all Ministerial Departments take part in Research and Development planning, worked out a National Health Programme within the framework of the National Plan, in which the Human Genome is considered a specific objective.The Interministerial Committee has also strongly supported the creation and launching of the corresponding programme of the European Economic Community. All this will undoubtedly contribute to the integration, subsidizing and cooperation of research, which by their very nature, is of utmost importance to projects such as the once we have discussed today.

The Spanish Administration is making great efforts to attain greater participation day by day in the international scientific field. These efforts are not isolated ones for the Autonomous Communities also devote important funds to scientific research. All this, together with the initiative of foundations such as the one that has received us today, is enabling the Spanish system of science and technology to grow in importance on a world-wide scale.

The creation of trained human resources is the most important wager for the development of science and technology. With this in mind, the National Plan for the Training of Research Personnel is enabling a great number of young scientists to be trained both in our country and abroad. To this end, I should like to thank the laboratories of the international community for their help and support by having opened their doors to our researchers.

All this is bringing about a new situation in the world of science and technology in Spain. During the hard times, our researchers, some of whom are present here, kept alight the torch that has today made Spanish science and technology important on the international scene. This is not a mere personal opinion: on the strength of bibliometric studies carried out, our advance in the world of science is quite clear.

To return to the Human Genome, I should not like to leave out the importance of this project and promise that we shall, within our limited resources, contribute to its development to some extent. Within this development, independently of the benefits it may bring to knowledge and its application to medicine and other sciences, there is its value and importance in contributing

to set up an ever-increasing internationalized system of science and technology.

Finally, I wish to congratulate all of you for having reserved an important space and time for the study of ethical and social aspects, as likewise for the importance of your conclusions.

Thanking you all very much.

José Angel Sánchez Asiaín

President of the Banco Bilbao Vizcaya Foundation

José Angel Sánchez Asiaín

President of the Banco Bilbao Vizcaya Foundation

It is a great privilege for me to thank you today for having honoured us by accepting to preside this Closing Session of the Workshop on International Cooperation for the Human Genome Project, of which our King is the Honorary President. On account of the ambitiousness of its scientific objectives, this project has aroused great enthusiasm, and at the same time profound interrogations on the social consequences to be derived from the broadening of our knowledge that the development of this projects offers.

For, to attempt ourselves to encounter the keys to understanding why we are what we are from the biological point of view, why our organism behaves as it behaves, also arouses great fascination, numerous and even controversial philosophical and ethical questions. This workshop has consequently been focused on confronting some of them on the basis of the excellent interventions of those taking part.

I wish to express my sincere admiration, respect and gratitude to Professor Watson, Professors Gilbert and Dausset, co-participants, in the development of certain essential aspects of this great project on the genome, all of whom were awarded the maximum distinction of the Swedish Academy of Sciences.

I should also like to express my admiration for Professor Santiago Grisolía, an outstanding biologist, winner of the Prince of Asturias Prize, and *alma mater* of this important encounter; my thanks too, to the Valencian Foundation for Advanced Studies and to all those who agreed to think together over the past few days on the ethical implications of this great project.

To attempt to understand the genetic basis of the human species is a thrilling prospect, not only for those who actively and directly take part in it, but also for the great majority of people who follow its development in admiration, albeit an admiration not free of concern. A concern that is of course reasonable. For this century has shown us that tools based on scientific knowledge can be used for alternative, and often counterposed, ends, because our world has also at times shown that it has attained an amazing capacity and perfection of means and tools at its disposal, although it has at times been misguided as to the end and aims that should be pursued. As Einstein said what characterizes our century is perfection of means and confusion of aims.

This does not prevent society from highly valuing science and technology, knowledge and research, as important enterprises in themselves, independently of their applications, on account of their value in improving our knowledge of the universe and our place in it. Society is also aware that many of the problems we face up to over the world can only be solved by means of a wise

applying of science and technology, nevertheless, this wise applying must be founded on an ethics of responsability, that is, in the conviction that we are responsible for the consequences, whether foreseeable or otherwise, to be derived from our acts and not merely from our good or bad intentions. This wisdom will also enable us to analyse and anticipate as far as possible the side-effects to be derived from applications considered at the outset as worthy of development.

And these dilemmas take on a singular force and relevance when we deal with disciplines such as biology, particularly the molecular biology entailed in the Human Genome Project. In the last years of this century they make up one of the fields of knowledge that are on the frontiers of scientific knowledge. This is because their discoveries can directly affect the human being's own physiobiological identity. And because any manipulation, intervention or information on this identitymay bring far-reaching consequences for the individual that may even affect both his or her own individuality and the esemble of links and relationships he or she has with society.

"The prospect of a genetic map, of a complete biological book of humanity, at one and the same time arouses enthusiasm and concern, giving rise to questions of an ethical and philosophical nature". This is textually stated in one of the central reports for setting up the Human Genome Project in the United States. And this concern for the ethical aspects of the project on the genome should oblige us to question ourselves on the direction and objectives to which our own research is channelled, questions to which certain answers have been proffered here over the past few days. *In any case, I think that the dignity of the human being is a mission and that respect for same must be an essential part of any research activity.*

For this reason, one should welcome the rise of a growing sensitivity to the ethical and social problems which scientific development brings. And particularly in the Human Genome Project, in which reflection on the ethical dimension runs parallel to development of research itself, and can therefore influence the later course of same instead of waiting for the first non-desired impacts to occur.

In any case, whenever new cognitive categories emerge, new perceptive approaches, new tools for the analysis of vital phenomena, that is, whenever the human being resorts to innovation as a driving mechanism, there occurs a double phenomenon of contestation on the one hand and practical application on the other, which notably affects a great deal of the structural resources of our society, whether these be scientific, political, socio-economic, legal or of any other kind. I also think that whenever these convulsions occur, the urgencies to innovate and the inertias to

preserve are usually rare in common forums of encounter, in time of joint reflection and compatible codes of communication.

And it is precisely this truly key function of providing environments of convergence, of supplying spaces for reflection, of offering the means for new horizons of reference to be explored and common compatibilities and languages to be sought, that is the true vocation of our Foundation, the BBV Foundation. For to create suitable frameworks to reflect at liberty on the great challenges of the end of this century, to interpret emergent situations through a new prism, and to achieve renewed systems of reference that allow for innovating voyages is without doubt the justification for all our efforts.

Therefore, our Foundation, either alone or in collaboration with other institutions, as in the case of this Workshop with the Valencian Foundation for Advanced Studies, will continue in its efforts to encourage, support and stimulate new pluri-disciplinary spaces for encounter and reflection. This, in order to offer the results to all strata of society as cultural paradigms, as elements of the new education society demands if it is to solve without violence its serious problems of identity and survival. For this information is an unrenounceable right of society, and it is one of the most important means to a person's beign able at each moment to make free decisions as to the direction and form to be taken by development and the technological applications of basic knowledge.

Madam: I should like to end by saying that it is of extraordinary value for science and culture, as for all of us, that the Crown should offer such exemplary understanding and support for the efforts of all those who, at different levels of science, work and strive to attain thresholds of knowledge to be shared with others, knowledge that leads to attemps at improving –from the innovation that co-exists with tradition– the conditions o developments of human dignity with the desire to attain a freer, more cultured society. My sincere thaks for this.

Many thanks to you all.

Julián García Vargas

Minister of Health and Consumer Affairs (Spain)

Julián García Vargas

Minister of Health and Consumer Affairs (Spain)

Your Majesty,
Ladies and Gentlemen:

On behalf of the Government of Spain, I should like to thank all scientists and experts who have intervened for their participation in this International Workshop, as likewise the support of the BBV Foundation and the hard work of its President, Professor Grisolía.

The highest praise is due to all of those who have made it possible for this Workshop to be held in Spain on the ethical aspects of one of the most wide-ranging ever scientific projects which even has the backing of UNESCO and the ECC.

I should also like to congratulate you for the approach that is being given to this ambitious task of analysing the human genome by carrying out the purely scientific work alongside reflection on its possible social and ethical consequences at one and the same time. Had this always been done in all fields of science, mankind could have been spared an era of fear and uncertainty which has today fortunately been overcome.

The scientific community and society have much to learn from this approach, which is based on inter-disciplinary dialogue, in order to solve the conflicts that arise between biomedical advances and ethics, with the fundamental participation of the citizens themselves. To be more precise, this dialogue must lead us to work out norms of behaviour in genetic research and its applications.

These norms can no longer be based on the ideal portrayed in Plato's *Republic*, which allowed the intellectual leader, the philosopher, to discern between the true and the false, good and evil, the just and the unjust.

The great revolutions of the modern era, the English, the American and later the French revolutions, suggested another, more democratic and symmetrical type of human relationships. These ideas are crystallized in the spirit of the Enlightenment, the defensor of the autonomous nature of the human individual, of the individual as subject who as such should be respected by all those who hold different moral stances, who must take an active part in the decisions or reflections that affect him or her. A modern philosopher and sociologist, Habermas, has updated this spirit by speaking of "communicative action", of this very participative rationality which is characteristic of our time.

In societies such as ours, with their framework of co-existence drawn out in the modern Constitutions that support ideological and social pluralism and the respect for human right, the relationship to be established between scientists, the individual and

society has become autonomous, plural, desacralized and conflictive.

Or this reason, in texts such as the recent Law of Assisted Human Reproduction of 1988, it is stated that there is no doubt that scientific research must continue its course and that it should not be limited unless this be on firmly based criteria that prevent it clashing with human rights and the individual's dignity, and that to this end an open, rigours and dispassionate collaboration is required between society and science.

This is the gist of the speech given to this workshop by Professor Jean Dausset, Nobel prize winner, President of the Universal Movement for Scientific Responsibility, who proposed to the Organization of the United Nations that an international Commission should be created to control manipulation of the map of the human genome.

As was to be expected, we are in Spain advancing in the same direction and consequently, with the State in the role of the inspirer of social articulation, we are working on the constitution of the National Commission of Bio-ethics, in which scientific, professional and social personalities connected with the sciences of health and biology are to participate.

The Commission will be responsible for informing and advising the Health Administrations as to security, efficiency, plausibility and ethical aspects related to the technologies relevant to health and medical assistance, as likewise with regard to the criteria as to limiting their applications.

The project of the Royal Decree this Commission has created is already written out and will soon be examined by a great number of public and private institutions for them to offer suggestions and ideas.

Your Majesty, genetics is a science of the future that can explain and solve many aspects of the biological process and alterations in people's state of health, but it also poses important questions.

Finally, therefore, I encourage you to continue to reflect on the questions which are still without an answer, so that all together this research will not only be of a very high scientific quality, but will also have the relevance for the human collective we all hope for.

Thank you all very much.

Joan Lerma

President of the Valencian Community

Joan Lerma

President of the Valencian Community

Your Majesty,
Mr. Minister,
Ladies and gentlemen:

As representative of the Government of the Valencian Community, I am honoured to be here today with you, for the Closing Session of this II Workshop on International Cooperation for the Human Genome Project, which has dealt with ethical aspects of same.

In the first place, on behalf of the Valencia Community, I should like to thank Her Majesty, Queen Sofia for being here with us today, Her presence certainly honours this workshop and sets it at the level fitting to it, once more displaying the interest of our Monarchy for science and culture, an interest that both stimulates and encourages us as we had the occasion to see recently when His Highness, the Prince of Asturias visited us for the awarding of the Jaime I Prize. I should also like to thank the Minister of Health and Consumer Affairs for attending today, and mention the distinguished scientists among us.

This is not the first time that Valencia has been the venue for an encounter of this nature. In October 1988, the I Workshop on the Human Genome was held here. These internationally important events have made our city and Community a scientific forum and act as a measure of how important we consider the development of knowledge in all fields and the advantages of a modernity invariably to be understood as at the service of society and its members.

The conclusions of this meeting have once more shown the quality of contemporary science, for which scientific knowledge must only be used in the service of the dignity, integrity and the future of human beings, Spain is fully immersed in the European and world-wide tendency to use technology rationally as a factor of progress improvement and the attainment of higher levels of equality and welfare, and the people of Valencia feel identified with this project. We therefore feel that it is important not to be left on the margin of the Human Genome Project, on which a competent research group of ours is working.

We believe that it is legitimate to try to make medicine advance by using genetic mapping, which opens up the way to knowledge and enables scientists to design and apply new therapies to diseases that had so far been resistant to the advances of medicine, such as cancer.

This must of course be achieved on the strength of presuppositions of a severely humanistic and social ethics, so that scientific discoveries do not get out of hand –as has unfortunately so often occurred in other fields. Self-awareness and self-limitation must govern science itself so that the inertia of its discoveries may not

lose sight of its objectives, which are none other than those of helping life to develop more fully.

Science does not possess the keys to human nature, neither do we believe that genetic mapping will reveal its secrets to us. The essence of human nature does not lie in genes but in language, for man is a fundamentally social being endowed with speech, that is, with thought, and is conditioned by his environment. One should not let oneself be led away by fantasy when dealing with these matters that are so often trivialized and subject to a banalization that magnifies them, to the detriment of their true role and dimension.

When this workshop was inaugurated, I said something I should like to repeat here. Ethics is an extremely flexible sphere; if it is individual, it may be subjective and hence arbitrary. Therefore, the only valid frame of reference in this field is the law. But the politician and legislator need the scientist to supply the information on the profound consequences of his discoveries before debating on their limits and establishing universally valid rules.

This makes meetings such as the one we are now closing have such extraordinary importance, for they take knowledge out of the laboratory into the grounds of debate, and because it is no longer the grounds of debate, and because it is no longer the microscope or the computer that is used in them, but speech, reflection and criticism.

My warmest congratulations to those whose efforts have made it possible for this to take place once more amongst us. We shall always be happy to welcome such distinguished visitors and hope that they too, you, have spent these days with us full of positive experiences.

Many thanks to you all.

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