FUNDACION BBV

The Human Genome Project: Legal Aspects

Volume I

in collaboration with

The University of Deusto and the Diputación Foral de Bizkaia

Fundación BBV has consistently worked to foster reflection and debate among experts as to the social implications of scientific development. One such Fundación BBV initiative was the International Workshop on *The Human Genome Project: Legal Aspects,* held at the University of Deusto in Bilbao in May 1993, with the collaboration of the Provincial Deputation of Bizkaia.

The exchange of viewpoints which there ensued between scientists and jurists richly justified the calling of the workshop, and bore out both the need to maintain a fluid dialogue between their two worlds, so that reasonable common conclusions could be reached, as well as the complexity of the various legal issues raised by human genome research results and applications. The conclusion was that our society must find the appropriate legal instruments with which to address these new human challenges. In this sense, the Bilbao Declaration, as the workshop's culmination, offers a minimum frame of reference and consensus.

This work contains more than 100 papers and talks presented at the workshop and in the roundtable discussions, thus making available texts of extraordinary interest which should help favour continuity in the reflection, study and formulation of proposals by legal experts.

This work is also available in a Spanish version. In both publications, Documenta has been greatly assisted by the Fundación BBV - Provincial Deputation of Bizkaia Chair in Law and Human Genome at the University of Deusto.

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The Human Genome Project: Legal Aspects

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INAUGURATION

Almost since its very beginning, Fundación BBV has been actively exploring the social implications of the Human Genome Project and its related ethical and legal issues.

One consequence of this interest was the workshop on *International Cooperation for the Human Genome Project: Ethics* held in Valencia in November 1990 with the participation of 36 experts. The workshop proceedings and papers were published in Spanish and English, the latter under the title "Human Genome Project: Ethics" and enjoyed a wide distribution among Spanish and international specialists in the field. Later, in May 1993, the Bilbao international workshop on *The Human Genome Project: Legal Aspects* brought together more than one hundred specialists from diverse fields and disciplines to analyze the possible legal implications of research and development relating to the Human Genome Project.

These first two volumes of the proceedings of the Bilbao workshop include, in addition to scientific and legal introductions by two leading specialists, the workshop papers addressing issues of advances in genetics and their implications for man's freedom, privacy rights, the culpability principle and patentability. Preparation is under way of the third and fourth volumes, which will include the rest of the papers presented at the workshop as well as a glossary of genetics terms.

We at Fundación BBV thus hope to make a significant contribution to the extensive documentation which has recently appeared in this field, with the papers, for the most part original texts, arising from the workshop, organized in collaboration with the Provincial Deputation of Bizkaia and the University of Deusto.

Fundación BBV wishes to express its gratitude for the enthusiastic collaboration in the workshops of some of the most prestigious Spanish and international names in the world of medicine, law, philosophy, and other important domains of human knowledge, who you will find listed within this work.

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OPENING SESSION OF THE WORKSHOP «THE HUMAN GENOME PROJECT: LEGAL ASPECTS»

Jesús María Eguiluz

Rector of the University of Deusto, Bilbao. Spain.

I do not wish my words to draw out the official opening of this International Workshop on the Human Genome Project and its Legal Aspects, which we are now inaugurating, or to run over into the time allotted to your discussion of these critical issues. But neither would I want to disregard the kind invitation presented to me on behalf of the Deputation of Bizkaia and the Fundación BBV by their senior representatives, Mr Alberto Pradera and Mr José Angel Sánchez Asiaín, the organizers and souls of this gathering, who are chairing this inaugural session. Their invitation allows me to wish all of you a warm and sincere welcome on behalf of the University of Deusto. Our University hopes that you will feel genuinely at home with us over the next few days.

It is certainly not for reasons of mere protocol that I take pleasure in the fact that this Workshop on law and the genome is being held in Bilbao, and at our University in particular, because, in addition to bringing all of you here, this conference has three features which I believe deserve to be highlighted.

First of all, this gathering represents a serious scientific and academic reflection on a subject of immense importance, with a nearly unfathomable but certain future, and of the utmost interest for our society. It combines innovation and humanism in that variegated and difficult balance reached between scientific development and the regulatory limits derived from a social order

based on human progress. Each day brings ever greater awareness that the Genome Project, in addition to its novelty and complexity, also raises prospects which must concern and, more importantly, be actively addressed by all members of our society, given the world opening up before us and its multiple repercussions, positive as well as negative, for the individual and society, with which you are more familiar than am I.

A second noteworthy aspect is the collaboration between different forces which have contributed to making this gathering possible, based on the type of interdisciplinary approach that is pivotal to successfully tackling the many problems facing modern man and society. Such efforts also enjoy the active support of various public and private institutions, as can be readily seen in this Workshop.

A third important feature, among the many which I could cite, is in my opinion the network which will arise from the Workshop. This insures that this Workshop will be more than a remarkable one-time social event that managed to gather together in Bilbao a truly outstanding roster of personalities and scientists, marking a continuity with the efforts born of previous such conferences, such as the one held in Valencia, which we hope will find a suitable platform for prolonging the service it does to our society. In this sense we are encouraged by the proposals along these lines put forward on many occasions by the organizers and sponsors of this momentous meeting, the Fundación BBV and Deputation of Bizkaia, as well as by support of the University of Deusto, whose core concern has always been in the field of law and humanities, as part of our mission to help satisfy the needs of society.

You will therefore understand that my joy in greeting you is not mere protocol.

I will conclude with words of gratitude, first of all to the Provincial Deputation of Bizkaia and the Fundación BBV, for making this important Workshop a reality and for choosing the University of Deusto as host and possible continuer of this effort; and my thanks to all of you, whose presence here presages vibrant days of discussion of the issues to be addressed here.

So many thanks to all of you, welcome to Deusto and have a nice day.

José Angel Sánchez Asiaín

President of Fundación Banco Bilbao Vizcaya, Bilbao. Spain.

My first words at this opening ceremony must be of warm welcome and effusive gratitude, on behalf of Fundación BBV, to all those who have contributed to the success of this International Workshop on the Legal Aspects of the Human Genome Project. In no way is this gratitude simply a matter of protocol. For the fact is that throughout the entire process of planning and organizing this meeting, Fundación BBV has enjoyed the collaboration, understanding, assistance and, above all, enthusiasm of all those scheduled to participate during the next few days to an extent beyond that which words of appreciation can acknowledge.

We have also benefitted from the collaboration of the Provincial Deputation of Bizkaia, which has always shown great sensitivity and concern in social, cultural and scientific matters. I believe its participation lends solemnity to this grand gathering of prominent persons from all over the world.

In such circumstances, and at the risk of being seen as overly optimistic, please allow me to describe this conference as of the utmost importance. It certainly is from the standpoint of Fundación BBV, which came into existence not very long ago with the stated mission of fostering forums for debate and shortening the distances between society and the driving forces and individuals who shape our common future. Also noteworthy is the interdisciplinary nature of this meeting, as well as the originality and

magnitude of the questions that are going to be addressed. This meeting is important because it will encourage us to reflect more seriously, in the light of what we now know regarding the origins of human life, upon the future prospects and alternatives facing humanity.

In mid-1990 our recently established Fundación BBV took the first steps in its quest to be of service to our society. On the recommendation of Professor Grisolía, member of Fundación BBV's Board of Advisors, we took the view that the ethical and legal implications of the Human Genome Project could enable us to play an active part in the world of intellectual discourse, establishing platforms from which to address the problems and uncertainties of our age. The magnitude of the task, however, counselled a preliminary meeting dedicated exclusively to the Project's ethical aspects, leaving analysis and debate of the related legal implications for a later date. Thus was born the Valencia Workshop on the Human Genome and Ethics.

Now, with this second meeting Fundación BBV seeks to examine the legal issues as a complement to the work of the first meeting. We want to place the responsibilities of law face to face with the responsibilities of scientific research and its applications in biology and in the Human Genome Project.

Contemporary society finds itself torn between the uncertainties of its limits and the hope of being able to confront those limits with sufficient foresight. Also, although science is usually applied in our best interests, the manner in which it is used is at times dominated by intellectual or political fashion rather than by a rational assessment of the situation. Hence, our society's misunderstanding of many of the ideas deriving from science. There are even occasions on which misinterpretation of scientific ideas has more sway than the original ideas themselves. In consequence, in some advanced societies the traditional admiration for science is being subverted and scientific discoveries are arousing apprehension, fear, even hostility.

In any event, the modern world must obviously address problems of progress and its consequences, including undesirable and hazardous ones. These are all the more tragic when they concern our very life as biological beings, the basis of all our essential values. Tissue transplants, *in vitro* fertilization, eugenics, the use of human gametes, experimentation with human embryos and the enormous cost of public health care raise not only legal but cultural problems in which it becomes increasingly necessary to separate hope from optimism.

We must recognize that the world we live in is not just the chance outcome of a natural order, but the logical unfolding of

the human essence. Wherever we go, we find no place untouched by the modern mind. On the basis of scientific and technological knowledge, the human mind produces, constructs, administrates and destroys. The world is now one in which man is constantly confronted by his own work; a world whose increasing reliance on scientific techniques is converting us into artefact.

In this artificial world we are less and less in a position to see ourselves within nature. Undaunted by any limits, science and technology now contemplate man himself as a new experimental theatre. One example, no doubt, is the insinuation by biological researchers that man's physical nature can be genetically engineered, just as man can be transformed by the physical and social worlds into an artefact of another kind. As far as the domain of human biology is concerned, there is no doubt about the importance now attributed to the possibility of interventions in the human genome.

In any event, problems associated with artificial insemination, *in vitro* fertilization and various other spectacular results in transgenic medicine are surpassing all expectations. We are making discoveries inconceivable only a short time ago. All this, and this is our subject today, is overflowing the traditional moral and legal levees, making it more difficult for modern society to achieve consensus on the legal and ethical limits of scientific and technological change.

At Fundación BBV, we believe all society must be urgently engaged in an interdisciplinary debate on these questions and that, furthermore, this debate needs to go beyond national borders. When the life of our own species is affected all over the world by its own brilliant progress in biology, international participation is of the essence for comprehending and managing the new situation. This is the idea that gave birth to the present International Workshop on the Legal Aspects of the Human Genome Project.

Reading the minutes of a recent Fundación BBV meeting on Science, Technology and Culture, I was struck by the words of the Honourable Judge Kirby, President of the Court of Appeal of Sidney, and today among us. He told us of how judicial efforts to control science are often left up in the air. «What makes society feel better,» he said at that last meeting, «is often nothing more than a temporary restraint. What science and technology teach us is that they will continue on their majestic course. I believe,» he added, «that we must be humble before these questions, for science to a great extent has its own momentum.»

That may be so. Yet, where the environment is affected, where basic social and political values are at stake, or where, as is the

case with the Human Genome Project, our own species is directly involved, humanity has the right, and the duty, to insist that moral dilemmas be identified and openly debated such that the corresponding decisions be made consciously, with input from all, and be enforced.

Society no longer seems to take heed of Dante's observation that «where God governs without intermediaries, natural law is not competent.» For today there are unexpected scientific developments that directly involve us and for which no obvious political or moral solutions have been found. All we can do so far is debate, and in the course of doing so bring together the various bodies of scientific and technological knowledge in the interests of nurturing responsibility and solidarity.

In this effort a special task falls to those –like the immense majority of the persons gathered here today at the University of Deusto– whom society has entrusted with the interpretation and enforcement of its laws; a special task and ineluctable responsibility, and, also, hitherto unimagined opportunities. These responsibilities emanate from the need to foster understanding and correct legal interpretation of the real scope and social implications of the Human Genome Project, its findings and its promises.

They have the opportunity to achieve, by means of the protective influence of human rights, the kind of cultural unity between science and practical reason which has so often been thwarted by lack of harmony between their respective competencies.

We find both responsibility and opportunity in the necessary and constant process of adapting our human laws to the new conditions of survival dictated by biology and other sciences. And also in the avoidance of the conflicts so often occasioned when the dictates of privilege are mixed with the dictates of solidarity, by collisions between private interests, or by the absence of new horizons of freedom and dignity with which to plurastically interpret the new realities and new paradoxes of the modern world.

Those paradoxes include the fact that modern scientific man, who aspires to be both maker and master of the world, must never forget that he himself belongs to that world. There is the grave danger that the agent of progress will become its object, not necessarily to the benefit of his prestige, wellbeing or happiness.

The modern lawmaker and jurist must also remember that the application of science and technology to human relations does not necessarily infuse those relations with more humanism. Regulating the process is not automatically equivalent to regulating and protecting man's humanity. Patenting a biological design cer-

tainly does not imply being able to patent man as the holder of rights, but neither does it dispel the danger of patenting it as an object of man's greed.

In conclusion, I wish to point out that Fundación BBV believes there is no better way to fulfil our mission of broadening the social commitments of the BBV Group than to encourage dialogue among the protagonists of the major undertakings shaping our society's future. What is needed is to shorten the bridges between such persons and society at large so that the decisions made ultimately be the fruit of all cultures, interests and creeds, while the traditional virtues of work, research, progress and competition be cloaked in the noble mantle of solidarity.

I believe that everyone present here, and certainly the Fundación BBV, is sure that the participants in this international workshop will make their utmost effort to arrive at conclusions which, although necessarily limited, will be sufficiently authoritative and vigorous to win acceptance and respect in our community. For society it becomes ever more necessary to have guidelines and references for examining its permanent and urgent dilemmas. We all hope that at its conclusion this meeting have will cast a little more light on these matters.

Thank you very much, and the best of luck in your efforts.

José Ramón Recalde

Secretary of Justice of the Basque Government. Spain.

I will limit myself to issuing a warm greeting and welcome to this workshop on the Human Genome Project. My knowledge of this field does not go much beyond an awareness of its importance. I would like to be present as a student, and will make sure to attend and listen in on some of the sessions.

Issues of this magnitude produce in me the vertigo produced by the questions posed by the great philosophers, such as Spinoza, on the relation between freedom and necessity, the concept of moral law, even the relation between the individual and the universal. And, apart from the foregoing, I will only cite my faith in the value and valour of scientists [1] as they take on the problems before us. As Ovid said: «while all animals or living beings look down to the ground, the Divine Creator gave man a face and commanded that he look to the heavens and fix his gaze on the stars». That is the mission of scientists.

[1] Translator's note: The speaker uses only the Spanish word *valor*, which has more than one English translation equivalent: value and valour.

Iñaki Azkuna

Secretary of Health of the Basque Government. Spain.

Just some very brief words to thank the Fundación BBV and its President, Professor Sánchez Asiaín, for organizing this exceptional International Workshop on the Genome Project. This is the second event organized by the Fundación in Euskadi during 1993. The other, as you know, was the Vitoria meeting on nutrition.

We in the health-care field regard the Human Genome Project with a mixture of respect and hope. Such is always the case with new fields of investigation and incipient projects; usually, the problem lies in the uses to which the discoveries are later put.

Only a few years ago we witnessed with amazement, and fear in the case of some, the age of transplants. Today they are routine. Now it appears that research is heading toward the use of animal organs; unthinkable a short time ago. Doctors, lawmakers, jurists, we have all had to make adjustments, and this has now been accepted positively by our society. The goal was worthy and no new Frankenstein emerged. Yet, humanity has known other extraordinary achievements that when misused can arouse unimagined destructive power.

Perhaps few research projects have such great implications for man as does the Genome Project, nor perhaps have we ever had such enormous possibilities to control –and I am speaking from the standpoint of health care– certain diseases. The benefits are

potentially extraordinary; so, too, the problems which might arise. But let us humbly recall that next Saturday marks the 40th anniversary of the first time man scaled Everest, which, after all, was and continues to be nothing but a mountain.

We all hope that the Human Genome Project will be taken very seriously and not meet with negative complications, something all too frequent in so many of the endeavours initiated by man throughout his long existence.

José Alberto Pradera

General Deputy for Bizkaia. Spain.

On some occasions, and often quite rightly, we politicians are accused of shortsightedness, of concerning ourselves only with day to day developments, of decisions and actions aimed solely designed for electoral gain.

The people voicing these criticisms are frequently right. It is also true, although it serves as no excuse, that citizens demand of institutional representatives that we act swiftly and effectively, and as you all know these two words are sometimes contradictory. This pressure on occasion leads us to lower our sights and concentrate on the short term instead of lifting our gaze toward the medium and long range future. And sometimes, what is most immediate, for all its urgency is not always what is most important.

I offer this small initial reflection so that you may understand the outlook of an institutional leader when he is told of the current importance, and above all of the future importance, of human genome research.

Nevertheless, from my first conversations with the President of the Fundación BBV and Professors Grisolía and Watson, I realized the enormous, and I think that is the right word, current and

future importance for society of genetic research and its scientific, ethical and legal aspects.

But as Goethe asserted, «with knowledge doubt enters». And I who speak to you here today wish to find answers to the many doubts which have come to my mind about the human genome after these initial contacts.

Thus, when José Angel Sánchez Asiaín raised the possibility of the Deputation of Bizkaia collaborating on the International Workshop on «The Human Genome Project: Legal Aspects» that we are inaugurating today, I did not hesitate for moment. Without forgetting our daily responsibilities, the immediate, official institutions must participate in and foster knowledge of the very essence of human beings. And on this occasion, my personal desires mixed with the political responsibility of moving forward in so pivotal a field for our society's future.

In 1990 the ethical aspects of the Human Genome Project were analyzed in Valencia, also under the direction of the Fundación BBV. In a few moments we will begin discussion of the legal implications of genetic investigation.

As was aptly stated by the President of the Court of Justice of the Basque Country the day this meeting was presented in the media, in this field the law is lagging behind reality. Perhaps, at least for now, it could not be otherwise. This is a good time to change this tendency and analyze the legal implications of the Human Genome Project insofar as its effects on fundamental human rights and a good many political and civil rights.

There is an urgent need for a legal framework that can safeguard genetic investigation while giving society security and confidence.

I am sure that this International Workshop on «The Human Genome Project: Legal Aspects» will produce resolutions of capital importance for the future. The intellectual and professional calibre of the participants convince me of this.

I would like to end my talk by thanking the Fundación BBV and its President, José Angel Sánchez Asiaín, particularly, for their efforts in making a reality of the maxim that «nothing of what is human should be alien to us». My gratitude also extends to the University of Deusto for its collaboration and for once again displaying its multi-faceted concern for the future.

And to all of you speakers and participants I wish you fruitful debates, for there will be many of us awaiting the Bilbao Declaration as a complement to the one issued 3 years ago in Valencia.

Thank you very much.

INTRODUCTION

SCIENTIFIC INTRODUCTION

Santiago Grisolía

Chairman of the UNESCO Scientific Steering Committee for the Human Genome Project; Distinguished Professor at the University of Kansas, United States, and at the Valencia Foundation for Biomedical Research.

I would like to second the gratitude expressed this morning to the Fundación BBV and also, of course, to the Deputation of Bizkaia and all the audience for your contribution to this important workshop.

The development of medicine and its transformation from a pseudoscience into a discipline based on experimentation and direct observation have proceeded very rapidly. True, genuine anatomy began with the first descriptions of Vesalio, physician to Felipe II, and his famous book *De Humani Corporis Fabrica*. Nevertheless, until the great discoveries of the 19th century, with such extraordinary figures as Virchow (pathology), Pasteur (microbiology) and Bernard (experimental medicine), medicine was fundamentally descriptive. The breakthroughs of the late 19th century and the half century now coming to an end, particularly the discovery of antibiotics and sophisticated diagnostic methods, began to make possible not just «band-aids» but genuine healing, for example, of most infectious diseases.

Meanwhile, and practically unnoticed, approximately one and a half centuries ago Mendel began his work, studying crosses of peas. Many years passed before Mendel's discoveries were to be

recognized at the beginning of this century by other researchers, among whom it is important to cite (especially for me because he attended my university) a young student named William Sutton who joined the ideas and techniques of genetics and cytology, thus giving birth to cytogenetics. Years later Morgan and his school, with their studies of vinegar flies, buttressed the foundations of Mendelian genetics and won it recognition.

The word genome was practically unknown early in the century. Winkler used it for the first time approximately 70 years ago not long after the term gene had been introduced in science. «Genome» initially referred to the entire set of genes of an organism, but today it is known that DNA has areas which are not genes but which no doubt are nonetheless of great interest. This is so true that the overall array of all these differing components has allowed some researchers to use the somewhat confusing term «genomic code».

Since the initiation of the so-called Human Genome Project, Dr Cook-Deegan has worked with all its «actors». He will give a detailed account of the historical aspects of what I consider as the Project's anatomy, that is, to identify all the genes, some 100,000, and to completely sequence the human genome. This immense task was first suggested in a pioneering 1986 publication by Professor Dulbecco proposing that a map of the genome would be crucial for discovering the pathology of cancer and its possible therapy.

The first international workshop for cooperation on the Human Genome Project was held in 1988 in Valencia. The Fundación BBV, practically since its creation, has been keenly interested in and pioneered international cooperation in the Project. The reason for this interest is that we regard it as a social commitment and because, even though Spain has excellent young biochemists and specialists in genetics, there is no national plan for the Human Genome Project. The Fundación BBV seeks and strives to foster debates on major issues, and certainly few issues can match the Human Genome Project in breadth and import. That is why it was thought important to initiate this dialogue, a long-lasting dialogue but one which cannot be deferred until after the Project successfully completes what I consider «stage A» or the «first stage», because a detailed understanding of the genome, that is, mapping the genes and the complete sequencing of the human genome, will practically never end. This detailed map will serve as the basis for subsequent studies aimed at understanding the interaction of genes, their controls, comparative aspects with other genomes, and, lastly, although much further along, all aspects referring to determinism.

Thus, the President of the Fundación BBV, Mr José Angel Sánchez Aisaín, decided to hold monographic meetings on different aspects of the Human Genome Project and requested my collaboration in organizing these meetings. I wish to take this opportunity to thank him for his confidence and his continued and generous support, all the more so because I am a biochemist and not an expert in genetics. The first meeting in 1990 was on ethics and this year's workshop addresses the legal aspects of the Project. Although intimately linked, there are legal aspects which may not be ethical issues and ethical aspects which are not necessarily legal issues. We are lucky that this workshop on the legal aspects is being held this year, as it thus coincides with the 40th anniversary of Watson and Crick's famous double helix proposal, considered by many as the century's most important scientific advance.

Although the initial part of the Project's development is now history and, as I said, will be covered by Dr Cook-Deegan, it is important to briefly discuss what can and should be done in this first stage of the Project. Thus, I want to stress that when the 1990 workshop was held, there were still many who thought the Project was a pipe-dream. Today we know it is a reality. Just as Vesalio's map marked the scientific beginning of medicine, the Project has buttressed the concept of preventive medicine and given rise to predictive medicine, as introduced by Professor Dausset; that is, medicine has made a quantitative and qualitative leap.

What has happened these last 2 years? What can be done in the immediate future? As examples of the advances I will remind you that human chromosomes have now been almost completely mapped. And that the polymerase chain reaction (PCR) is no longer a highly specialized technique and has now become perhaps the most common technique in most laboratories, including clinical laboratories. On the way here Professor Gajdusek told me of how it is already extensively used in Cuba, as he had occasion to observe on his recent visit.

Recall that one out of every eight or nine women currently suffer or will suffer breast cancer. Dr Mary Claire King, who addressed us at the 1990 workshop on the use of mitochondrial DNA to identify children of the mothers of the Plaza de mayo, already then announced the first indications of a breast cancer gene. Although her studies were initially greeted with scepticism, they have been confirmed and we are very close to locating the gene in chromosome 17, which will permit reliable diagnosis in 5% of breast cancers.

It has been recently found that the number of triplet repeats is much greater in certain diseases such as the fragile X chromoso-

me syndrome, myotonic dystrophy and vulvar and spinal atrophy, and that it increases in successive generations. Moreover, more recently, large numbers of such repeats have been found in much more common diseases such as cancer of the colon. This also appears to be the case in Huntington disease, the gene for which has been recently pinpointed, after its initial location 10 years ago, in segment 16.3 of the partial arm of chromosome 4. Curiously enough, it has been suggested that the onset age is also related to the increased number of repeat sequences. I stress this important discovery because it is an example of cooperative research. Thus, the paper which appears in the March issue of *Cell* was signed by the Huntington Collaborative Research Group.

As I have recently stated, Europeans, the French in particular, are making extraordinary advances. They were responsible for creating the European Gene Therapy Association, an organization which owes it origin to the efforts of the brilliant and indefatigable Dr Odile Cohen Haguenauer and to the generosity of the distinguished professor Michel Boiron. The outstanding aspects of this medical application, which originates with the Human Genome Project, were discussed in the first meeting of the European Working Group on Gene Therapy (Chateau de Maffliers, October 1992). Great emphasis was given at that meeting, and also more recently by other research centres, to the use of maternal cells. A proposal has been made for the creation of umbilical cord banks, given their rich content in maternal cells which have many advantages in clinical use.

In late 1992 a meeting at the Paris headquarters of UNESCO already noted the excellent advances being made by the «Genethon» group. Later, in April of this year, at the brilliant workshop organized by Dr Bernardi, also at the UNESCO Paris headquarters, «one of the most exciting parts of the workshop», as has been said by *Nature* in its April 29th issue, was Cohen and Weissenbach's presentation of findings on recent progress in the physical genetic mapping of the entire human genome. Dr Cohen has made extensive use of the so-called yeast artificial chromosomes or YACs.

As I expect Dr Schlessinger will mention, YACs, despite their problems, are very useful. As Dr Watson has said, we should not pay attention to «what has been criticized by some authors of lesser standing». In this regard Professor Venter will inform us very shortly of his extraordinary advances in cDNA sequences. These techniques will allow the first part of the project to be achieved much sooner than was previously thought, especially if the new chip technology, that is, hybridization sequencing, is resolved quickly, as I expect it will. This will potentially increase DNA sequencing by a factor of approximately 100 or more and

we will perhaps hear more on this from Dr Southern this morning.

I will next give a brief overview of the scientific basis of the Project and its social projection. As a physician, I will stress the new medicine which is now commencing.

All living beings have a genome. In the case of human beings, our genes, some 100,000, are found in a double strand of DNA of enormous length, for, as I have said, it is made up of some 3 billion chemical components. These chemical components are abbreviated by their initials A, T, C and G, which refer to two purines, adenine and guanine, and to two pyrimidines, cytosine and thymine. All these compounds, which are also referred to as bases, are linked to a sugar, the deoxyribose and to a phosphate as well; that is, base deoxyribose phosphate. The two strands made up of these substance are paired together forming a helix such that wherever there appears an adenine in one strand, a thymine faces it on the other, and vice versa. The same occurs with guanine and cytosine. All genetic information is contained in these strands. A gene is a fragment of a DNA strand.

Genes are expressed, that is, they generally manifest themselves in the production of our constituent proteins. A large portion (around 90%) of the DNA strands contains no genes and little is known as to their function. Nevertheless, their variations permit unequivocal identification of persons, given that although we are very similar (around 99%), we are all different.

When a gene is altered, sometimes very slightly, the result may be inconsequential or, depending on the area, lead to disease. Thus there are some 4000 diseases known to have their origin in a single gene. Some are very serious like Huntington disease, cystic fibrosis or pigmentary retinosis. What is more, there is clear evidence that a large part of diseases such as diabetes, mental disorders and possibly all diseases have a genetic basis. Now, since we are all different, it is only natural that the environment affects us differently as well and that the response to drugs varies widely from person to person. This, for example, is one of the great challenges and advantages of understanding the human genome.

In a somewhat arbitrary fashion we may divide the most immediate medical applications of genome knowledge into diagnostic and therapeutic uses. The latter can be subdivided into direct (genetic therapy per se) and indirect (drugs) uses. It should be made clear that the new predictive diagnostic techniques, including genetic counselling, also have an indirect therapeutic component, for example, the recommendation to not expose susceptible persons to certain hazardous environments in factories.

Naturally, knowledge of the genes, their sequence and especially the proteins produced by their expression will allow the development of new medicines aimed at specific cases.

Examples already exist, such as receptor inhibitors in the stomach which have practically done away with ulcers of this organ. Foreseeably many more such drugs will be found in the very near future, not only ones which block receptors but also those that stimulate receptors, above all in the central nervous system.

Due to time requirements and because of its novelty, the rest of this summary will be dedicated to the gene therapy which is now dawning. As is well known, it is generally agreed that gene therapy in somatic cells does not pose ethical problems, and is in no great way different, say, than surgical replacements. But there is great reservation with respect to applying such therapy to germ cells.

Nevertheless, whether by genetic counselling or therapy, it is important to cut down the ever increasing number (due, paradoxically, to medical advances and the high standard of living) of persons with monogenic genetic diseases, who already number more than 2% of the population in countries such as Spain. This assertion has solid ethical and economic grounds. In addition, there is clear evidence that when the number of repetitions of an altered gene increases in successive generations, the severity of certain diseases such as myotonic dystrophy also increases, as I have already indicated.

Historically speaking, as Friedman, a pioneer in this field, pointed out at the 1990 Valencia international cooperation workshop dedicated to the ethical aspects of the human genome, the concepts and technology of genetic engineering applied to therapy have in approximately two decades gone from quasi-science fiction to the commencement of clinical use.

No doubt Dulbecco's laboratory studies and their extension by Berg were crucial, demonstrating the production of a «chimera», that is, the fusion of virus SV-40, which converts cells in some animals into cancerous cells by injecting its DNA, with a bacteriophage, that is, fusing the DNA of two distinct species. The success of these and subsequent experiments was based on the recent understanding of the restriction enzymes which allow precision cutting of DNA into fragments. Gene manipulation techniques have now become commonplace after these experiments.

It should also be recalled that laboratory successes prompted one researcher, Cline, to prematurely apply these techniques to modifying cells in patients suffering from thalassaemia, a very serious disease caused by globin deficiency. As he could not conduct this

work in the United States, Cline used Israeli and Italian patients. The result was a therapeutic failure but nonetheless served to underscore the need to have as full an understanding of the problem as possible and submit the protocols to committees for their detailed study prior to their introduction in clinical practice.

Indeed, to convey an idea of exactly how seriously these protocols are taken, last December 28th the Director of the American National Institute of Health (NIH) approved a protocol for a woman with brain cancer known to have but a few months to live. The procedure consists of treating her with a vaccination made up of her own cancer cells genetically altered to produce interleukin-2, an immunological stimulant. Animal studies suggest that cancer cells which produce interleukin-2 are capable of attacking tumours in any part of the organism. On January 14th of this year Dr Healy called a meeting to decide the rules for such so-called compassion cases. Despite her highly altruistic interest this triggered a very strong critical reaction of the Advisory Committee on recombinant DNA, whose go-ahead, together with that of the Food and Drug Administration, is required (normally taking months).

There are currently several protocols under way, not only in the United States but also in Europe, where, as we have said, a gene therapy association has just been created. New ingenious paths are being developed in Europe and the United States.

Schematically speaking, gene therapy consists in compensating for an abnormal gene with a normal one to handle the functions of the defective gene, usually some kind of protein synthesis.

The necessary requisites for most diseases eligible for gene therapy are that:

a) there be only one defective gene;

b) the critical DNA sequences be known, particulary the regulating sequences which permit its expression;

c) there exist an effective system for introducing the gene;

d) it be used, given the high costs involved, in very serious diseases for which no alternatives exist.

One major ethical, legal and economic problem will be to decide, in light of its high current costs, who can or should benefit from this type of therapy.

I will end my talk here in order to be able to keep to the schedule. The book to be published with all the papers will include a brief glossary of the scientific terms used in the upcoming talks and papers, as well as the ones I have used in mine.

I will now turn the floor over to my friend of many years, Professor Villar Palasí.

LEGAL INTRODUCTION

José Luis Villar Palasí

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The coming together of two powerful wills, that of a leading scientist, Professor Grisolía, and of a foundation born with a clear vocation of service to society, the Fundación BBV, has spawned this debate on Law and the Human Genome Project, a followup to the Valencia conference of 1990 on the ethical aspects of these questions. The fertility of this meeting justifies this encounter of jurists with the Human Genome Project, which I confidently hope will be as fruitful, at least, as the one held 3 years ago.

This fortunate occasion allows me to be reunited with Professor Grisolía, whom I have personally known more than half a century, dating back to our hometown Valencia during the eventful years of the 1930s.

The discovery of the genome, the sequencing of its components, an understanding, in short, of what it is and how it behaves involve answers to basic inquiries. It should be pointed out from the outset that Spanish research in this field has succeeded in reaching a critical development threshold, thanks to scientists like Dr Grisolía who are an emerging island of whom we may rightly feel proud. Spain has not exactly displayed a penchant for basic science, particularly in a field of such current importance relevance that rare is the day in which the press does not report some new genome-related therapeutic application or discovery. Let us

openly recognize that the genome is in fashion, not only at the scientific level, but also popularly, constituting part of that ethereal concept we call popular culture. We may envisage that it will now have a permanent place in the general interest. A few weeks ago, newspapers were filled with concern over the IEB (Institute for Biological Studies), the future of the Centro de Biología Molecular of the CSIC (Molecular Biology Centre of the Spanish Higher Council for Scientific Research), and the Human Genome Diversity Project.

Basic science pursues bare knowledge, pure understanding, with no bounties, and that is its most praiseworthy virtue. The pure scientist does not worry about the possible future implications of a given discovery, he or she is satisfied with simply knowing. However, almost *pari passu* with this knowledge, there inevitably arise repercussions for daily life. The eternal clash of priorities may appear. Still, this is not the greatest of the resultant worries.

The trouble arises when basic science is joined together with its applications. Above all if you pause to reflect on the accumulation of solutions that are already being offered, even before the genome has been completely sequenced, by the knowledge of these sequences. The early detection and curing, or even prevention, of hereditary and degenerative diseases hitherto incurable by traditional therapeutic means, the birth –going beyond the human realm– of transgenic animals (such as pigs with human genes, obtained in Cambridge, in order to use their organs in transplants, or transgenic mice for which our ICEMA filed a patent application less than a month ago), or transgenic plants, are already a reality which presents itself as a preliminary vertex of an entire cosmos of scientific, medical, and biological mutations that will revolutionize science and society in all respects.

For the jurist, the genome and its understanding raises questions as to the very essence of free will and the imputability of responsibility, while at the same time suggesting previously unimagined solutions. Thus it is not solely a question of problems, but of problematic solutions. Consider, for example, paternity testing or evidence based on genomic analysis of trace evidence in criminal cases. The probability of full proof has reached percentages which mathematicians calculate as having 99.99% certainty, particularly with respect to negative proof, for positive proof is still far from conclusive, given the basic identity of all human substance. For the jurist, all things considered, this probability percentage resembles full certainty, a *probatio violentissima* to use the canonical terminology. Much more certain than witness testimony, to which may be applied the old Russian saying: «Nothing more uncertain than the truth as told by an eyewitness».

There are questions of civil law concerning capacity or responsibility, of commercial law, regarding insurability of foreseeable risks, of patent law, with respect to ownership and trading in knowledge and data, and of administrative law, such as the respect for privacy rights. And there are questions such as the one recently raised in the United States over whether a genetic defect detected during a military service medical examination should be disclosed to the interested party. Conflicts between fundamental personal rights (the right to privacy vs the right to health) are not unusual or unprecedented (see *inter alia* the October 20th 1992 Judgement No. 169 of the Spanish Constitutional Court, which cites other rulings), but here prior knowledge of the genome is going to generate easily predictable conflicts of unique scope. On being told of our genome defects and risks, we could lapse into a society of hypochondriacs.

And lastly, but not finally, the transcendental question of what is normal and what is abnormal; and of the dividing line there between. Most great men were so because they returned with interest the risk of a physical deficiency. The case of the pebbles in the mouth of Demosthenes is not the only one. The greatness of man perhaps resides in the overcoming of his defects, or of their compensation in other areas. There is probably more grandeur there than in correct use of the gifts with which we have been generously endowed by nature. To administrate well what is scarce or defective, make use of seeming disadvantages, entails more depth and greatness than the proper administration of talents. Especially because the limits between disease, defect and predisposition are far from being clearcut.

The triplets of chromosome 12 have been completely identified and sequenced. But it is in other chromosomes where a series of degenerative diseases have been located (4: Huntington's Chorea; 5: familial colon polyposis; 7: cystic fibrosis incidentally, with methods now considered primitive and artisan; 11: aniridia; 13: retinoblastoma; 14: precocious Alzheimer; 16: Marfan syndrome; 17: Von Rewlünghausen neurofibramatosis and possibly breast cancer through the so-called BRCA1 locus; the X chromosome (XLA) agammaglobulinemia). The professor has told us of diseases whose causes at the genetic level we are only now beginning to learn (muscular dystrophy, thalassaemia, hypercholesterolemia, pulmonary emphysema, mental retardation) which may be located in the fragile X chromosome. As we can see the panorama is vast.

A genetic defect may or may not provoke the specific disease with which it is associated. Here is the greatest difficulty of the cause-effect relation and where we are challenged by problems

at the borders of biochemistry, problems which demand the integration of other perspectives.

Returning to our line of argument, it is precisely this applicative vector of knowledge and manipulation –which runs from agriculture, ecology, the very anthropology of human evolution (the search for Eve, for genetic searches are surely in the female line), livestock, and its productivity, to human therapeutics– which poses a new challenge for the jurist, that is, the need to once again reconsider the very foundation of the techniques and categories with which jurists have traditionally operated. For artificial alteration of genes can give rise to unsuspected hazards for offspring and the environment. Hence the need to draw a line between genetic cures and improvements, the prevention of a disease or of a presumed defect, in short, between what the jurist considers admissible and the forbidden.

Western law issues from a continual response, dating back over 2,000 years of common history, by its foundations to the unrelenting changes of outlook and new phenomena which life in common and diverse world outlooks have produced in the form of a permanent, incessant challenge. Law, our western law, has hitherto demonstrated enormous flexibility and capacity to adapt. Let us not forget that from the times of Ulpiano until the present perhaps nothing has changed less than man's consciousness, while his environment, world view and the very axiology which necessary frames human life have undergone enormous change and upheaval. Nothing is irrelevant to the jurist, however intricate the paths of scientific knowledge. It has been rightly said that a jurist who only knows law knows nothing, not even law. For law is the fruit of the clash between actions and normative behavioral precepts, hence the accelerated mutability of its content in our times.

The penetration of religious ideas in law, more or less camouflaged, the emergence of nations and of states, the Renaissance, Enlightenment, capitalism, industrialization, international trade, the demographic explosion, the idea of democracy, the rise of the rights of man, concern for the environment, all marked frontal clashes of this kind. They all buffeted the old edifice of legal categories and techniques, which would not have been able to spawn what we jurists somewhat proudly call our system of law had it not been for its enormously flexible and fertile conceptas.

The debate which brings us together here and now attempts to elicit doubts and offer a response to the major upheaval which genome knowledge will generate –and is already generating in some fields– in our venerable legal system. Our system has endured thus far by continuously recreating itself, moulding itself like skin to the body. Suffice it to cite the new techniques relating

to commercial, maritime, banking, community or international legal relations. The autonomy of will, freedom, imputability, responsibility, probative technique, continue to stand as the pivots, nuanced over time, on which our law, our doctrine and our current practice turn.

Genome knowledge and, above all, the possibility of manipulating the genome is already buffeting this entire *jus receptum*. Certainly legal categories are flexible, but the very idea of responsibility begins to crumble when we jurists are told that a given genome sequence, a genetic defect we might say if Professor Grisolía will allow us to use our more conventional and traditional language, entails a predictable conduct: that insanity, alcoholism, drug addiction, sexual perversions, aggressiveness or violent tendencies, hyperactivity and criminogenic factors are there, in the human genome.

What then is left of freedom and responsibility?

Similar questions reach back as far as Beccaria and Lombroso, not to mention here the anguished theological polemic of predestination and the human condition, which were actually the precursors to the posing, and perhaps to the solution, of an eternal query.

The formidable truth is that now it is no longer a question of advancing theories but of recording something that is verifiable. For my part, I believe *ad exemplum*, allowing myself here a minor aside, that our legal system, in its setting down of the public law concept of financial liability, marked a considerable advance over the venerable ideas of *culpa in vigilando* or *in eligendo* of intermediate law, which in turn extended to previously unimagined limits the idea of vicarious liability.

As a jurist I am optimistic that our scientific establishment will be capable of adequately responding to the challenge now thrown out to us by science. A challenge which goes further, much further, than those which traditional legal doctrine addressed and resolved, in my opinion with unique success. But now basic science is crossing unknown and unpredictable thresholds, already spawning applications in many fields and in foreseeably many more in the not too distant future. If the very idea of freedom is called into question, then we must examine and attempt to offer new solutions –on a human scale– which reset law on new foundations that at least conventionally conciliate law with the new idea of freedom and imputability. Without these no law, social order or dignified life is possible. Unless we wish to install Aldous Huxley's *Brave New World*, which rests its predictive fiction on the absence of law and rights for others. I understand this issue to be the

central concern of this debate, with respect to which all the other problems here discussed, however important they may be, and they are very important, are merely secondary.

The eternal problem itself of human responsibility is being called into question. But we jurists may console ourselves by noting, before any other consideration, that man's responsibility has received and receives radically different responses depending on whether the answer comes from a theologist (Is there a standard theologist? Would it not be more correct to say that there are as many theologies as religions, sects, and even as many as there are individual theologists?); from a philosopher (to whom the same questions could be applied); from a psychologist, from a physician (and within medicine, from a psychiatrist, an endocrinologist, or a brain researcher or dietician and *sic in infinitum*); from a pedagogue (depending on the countless schools and methods of analysis), from a criminologist, or from a politician. I will not expound further on the abysmal disparity of responses to criminal fault, crime and punishment. They relate to something innate in the education received or denied. To the social setting, family, environment, epoch, habitational *ghetto*, social pressures, mass media, permissiveness and thus *usque ad nauseum*. It only demonstrates the relativeness of all things human and of the immense human capacity for explaining and/or fabling.

The arrow of time is usually said to be irreversible (and theologists normally tell us that the past is a limit on infinite divine power). Those who think in these terms are unfamiliar with the historians who have been making and remaking the arrow of time for centuries.

I will now return to the central subject, nothing more nor less than the genetic code, map or chart, the discovery of which will put us on the trail of our most intimate secrets, even of our life clock, as it has been graphically called.

And in this context, the related questions: the acceptance of an insurance contract, when this code is known and the element of chance therefore disappears from many such contracts, converting them into sure bets; personal identification by means of genetic testing (not a future issue, but a fiercely current one); the implications of genetic knowledge for labour relations; the right to genetic privacy, still to be defined. And two extremely delicate issues: the limits on genetic manipulation and the patentability of genetic discoveries [1]. And a host of other questions: genome use

[1] See the magazine *La Ley* of September 22nd 1992, where it says: «...doors will be opened to the patenting of genetic material and, even, of other superior forms of life as recently occurred with the patent of the onco-mouse or

in paternity testing [2] or for purposes of criminal evidence (see the October 20th 1992 Judgement of the Spanish Supreme Court).

Consider the enormous outlays involved in basic research. Certainly, pure engineering, robotic and computer techniques, essential tools of basic science, are a different matter and perfectly patentable. The ethical and legal problem turns on the question of whether or not the human genome or its fragments may be patented. The same occurs not with that which is identifiable with basic science –the identification of the «stick of fragment» of the active human genome– but with the product or path: the growth hormone is as patentable as are insulin drugs.

All these issues fall within this debate, from which we confidently hope will issue brilliant solutions that once again evidence the fertility of law, however disconcerting –and this time they most certainly are– the challenges thrown up before it.

The denial of patentability –a *prima facie* defendable conclusion– eliminates the incentives for investment. The two poles of this difficult dilemma are not easily reconciled.

Law as a system is one thing and the reaction of positive law another. The latter tends to resolve –somewhat naively– new challenges with new laws, sometimes promptly upon request, including with measured or single-case laws, or by rehabilitating the old *referé legislatif* system for all judges, or particularly for high courts. Or by recurring to higher jurisdictions or higher levels (the old Arrêt de Reglement) or recurring to fundamental principles, principles of legal regulation by analogy. In any event one thing is readily foreseeable: the solutions are unlikely to be national and must be internationalized. Our world is growing ever

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"Harvard mouse". This patent, eventually admitted by the European Patent Office, has no force in Spain as the application was filed prior to our adhesion to the European Patent Convention». In the United States, the Patent and Trademark Office eventually ruled against the patentability of human genome sequences. And even President Clinton has openly voiced his opposition to the possibility of patenting parts of the human genome. The 1992 Nice Congress pronounced itself along the same lines. It must be remembered, however, that a patent was issued in 1973 to a genetic recombinant technique, marking the beginning of the modern biotechnology industry. In late 1984, Bayer, under license from Genetech, assigned the exclusive rights to develop the genetic engineered Factor VIII. In 1989 Bayer and its subsidiary Miles began the process of manufacturing recombinant Factor VIII, for the treatment of haemophilia A, using genetically modified hamster kidney cells.

[2] Cf. Jaime de Castro García: *El principio de investigación de la paternidad y su aplicación jurisprudencial*, [The principle of paternity investigation and its jurisprudential application], *Estudios de Jurisprudencia*, Rev. Colex, Year II, n.° 4, January/February 1993, citing *inter alia* the Judgements handed down until said date.

smaller. For this and for so many other obvious reasons, the collaboration of jurists in this debate is welcome and remarkable.

So far some initial introductory words, but Rafael Mendizábal, whose requests I do not decline, asked me to expound at greater length. Forgive me then for what follows, which is only my compliance with this request, surveying extra-legal thoughts on the genome. The strictly legal interpretations will be the subject matter of the papers and talks by fellow legal experts, on whose turf I do not wish to tread.

We raise the issue in complex terms, and if we proceed intelligently we may perhaps obtain simplicity.

As Frank has said, the concept of simplicity, sometimes invoked for aesthetic reasons, is difficult to comprehend. The history of science reveals that the most important aspect of simplicity is the fertility which it affords. The world is not simple, but tremendously complex. Simplicity is nothing but the result of a difficult intellectual task of comprehension and the very term comprehension alludes to an artificial concentration of knowledge.

If we investigate which theories have won preference because of their simplicity we see that the reasons behind their acceptance were not economic or aesthetic, but dynamic. One theory is preferred over another because it is better suited for extension to unknown terrain: correspondence of theory and verified facts, logical relation between that theory and the rest of the body of knowledge. And lastly, there is its heuristic value, that is, the fertility of that specific theory vis-à-vis the rotten fruit of other approaches.

In passing we must point out that all fundamentalisms, be they scientific, religious, aesthetic, legal or moral, are infertile and even counterproductive, for it is the totality of different outlooks –existing and potential– from which the full meaning of the world and life can be derived. It is therefore not surprising that the concept of law amphibiologically serves science and jurisprudence.

Every age may be defined by its science, or by its law, as it may be by its political ideal or its music, or its aesthetics. There is nothing but different perspective and ways of seeing the same subject-object. With the particularity that the observer observes himself. And that alters the result of the observation, falsifying it in a way, falsifying the river of life. Hence the sceptical realism of modern man, who parting from the knowledge of the little which is known with any certainty enormously expands his scientific panorama. There is no definitive theory or conclusive law. Everything is open knowledge in an open society, and this very idea

«open society» is already significantly freighted with references, although the connotations to which I am alluding here now are tied to something much broader.

Precisely this past month a tribute was rendered to René Thom and his holistic conception of knowledge. And it is on that level which I would like to redirect my train of thought. Because I believe that all structures –be they physical, informational, mathematical, biochemical, linguistic or legal– as structures have something in common, to the extent to which the structure is systematic, alive. The application of the adjectives artificial or created to a systemic structure is itself artificial, deleterious, sterilizing. And I think a certain intercommunication is possible between the results and methods of approach to all systemic structures. Hence what follows now, where I put forward some considerations on presumed coincidences. Some are mathematical and surprising. Others refer to stimulating research into structural types, which for me have something in common uniting biochemists with jurists and with experts or students of other scientific fields. For all science is one, with an infinity of outlooks. It is the conjunction of all of them, which may perhaps allow us a total and more fruitful view of each field. This is the reason why in this encounter of biochemists with jurists, as with the earlier one on ethics, there should be no end to reciprocal grafts and buffeting challenges to the other sciences. The truth is that there are may strains of fundamentalism –including the scientific one– which are nothing but direct heirs to Platonism, as has been pointed out by André Glucksmann [3].

All science degenerates if submitted to prolonged isolation. Conversely, science gains in fecundity and life when it interacts with other systems. Mathematics, particularly statistics and correlations, have opened up new horizons for medicine, and specifically for biochemistry. But the new mathematics of complex automata probably serves to best explain the dynamics of cell life, despite its only recent creation (almost imagination).

Beginning with Arehytas Greek mathematicians had already brought together all that rests on number and magnitude. Music and number, medicine and magnitude began to live in interrelation when previously they had been regarded as isolated worlds. Something similar is taking place with science today. Physics is inconceivable without mathematics, nor does the latter harbour absolute truths, but only ones in a certain sense redundant. And the genome itself is after all nothing but a sequence of triplets,

[3] *El undécimo mandamiento. ¿Es posible ser moral?*, Spanish version in Península, Barcelona, 1993.

with a geometric form in space. There is still a Greek word which can be dually translated as to reason or to calculate [4].

Here we must consider the major contribution of mathematics to physics and to medicine itself, where it has entered the curriculum as an extremely useful tool. And the same occurs with the genome and law. It not only raises new problems –something which law has assimilated throughout the long course of its history– but affords plausible solutions. The relation is thus bi-univocal, bi-directional.

Allow me to mention something which I consider of utmost interest that I read in *Who occupied Einstein's Office?* (Ed. Regis, Anagrama 1992, pp. 147 and ff).

As for the self-reproduction process per se, let us suppose, Von Neumann said, that floating around in the sea of pieces there are two excellent central pieces or axles, and that the robot –which is also afloat there– needs them in order to make a copy of itself. Let us also suppose that those axles crash with the sensory organ of the robot, which assembles them.

The robot does this one time after another, following a preestablished plan, and we soon see a skeleton emerging from the sea of pieces where before there had been nothing but a collection of floating pieces. But the question is: where does the robot get its «plan»?

Let's see. Since the robot has sensory organs, it can learn the structure of some object –or even its own structure– by merely touching it, and then recording the essence of that structure in some kind of code. It could later use that same code as a guide or blueprint for making another version of the object in question. With respect to the code, Von Neumann applied a tool of Alan Turing's, who had discovered that any set of plans or instructions could be expressed by means of a binary notation, that is, by a simple string of ones and zeros. Basing himself on this, Von Neumann proposed that his automaton use a binary code and demonstrated the way of making a binary tape with the axles or central pieces afloat in the surrounding sea...

Once the structure of some object were written in code in some plan or blueprint, it would be easy for the automaton to duplicate the object described by the code. The automaton would read the

[4] In Plato: *The Republic* VII, 25. Supercomputers and Andrew McCammon's so-called computational biology are working on the genome world at Houston University's Kerk Center for Computational Biology in parallel with Rice University and the Baylor College of Medicine, in the same city.

blueprint in the binary tape, select the necessary elements from the sea of floating pieces surrounding it, and then assemble them according to the blueprint instructions. The result should usually be a perfect copy of the object in question.

This, of course, would not be self-reproduction, unless we imagine the automaton has learned its own structure and set it in code in the blueprint. In principle, there is no obstacle impeding the robot from doing so. Self-reproduction could therefore happen in the following manner. First, we have the known facts: the automaton itself, the sea of pieces and the blueprint. What is more, we have the mechanism which will make a copy of the blueprint. And, finally, we have a controlling organ that will guide all operations, ensuring they are carried out in the appropriate sequence. That is when the process begins. Following the blueprint instructions, the robot picks out the pieces it needs out of the sea of pieces: rigid axles, muscle parts, random organs and so forth. It gathers some things and separates others. It disposes of the axles, organs and everything else according to the blueprint instructions so that the object structure reproduces the robot's own structure exactly. In the final stage, the robot makes a copy of its own blueprint and places the copy in its offspring, thus giving rise to an exact copy of the parent robot. We have witnessed mechanical self-reproduction.

The curious thing about all this is that the way in which Von Neumann outlined self-reproduction coincides with the very method used by mother nature in performing the same task. Von Neumann elucidated his abstract analysis of machine reproduction in 1949, 4 years before Francis Crick and James Watson, explained the function of the DNA molecule. Let us recall here our Nobel Prize winner Severo Ochoa.

It turns out that DNA molecules are reproduced in exactly the same way that Von Neumann believed would have to be done by any self-reproducing machine.

As Freeman Dyson has explained in his autobiography *Disturbing the Universe*: «Now all high school students learn the biological identification of Von Neumann's four ingredients». The same automaton that takes care of duplicating the machine is the equivalent of the cell ribosomes, the particles which translate genetic information into protein molecules. The copying mechanism, the part of the robot which makes a copy of its own blueprint, is the equivalent of DNA and RNA polymers, the substances which combine nucleotides (rigid axles) to form longer chains of nucleic acids (the initial binary tape). The controller, which directs the robot operations, is the equivalent of the repressor and enhancer molecules that regulate gene development so that different cells

develop in distinct ways. And lastly we have the blueprint itself, which contains in binary code the robot's structure. This is the equivalent of the genetic materials, DNA and RNA, which contain the genetic code.

According to Dyson, «as far as we know, the basic design of any microorganism larger than a virus is exactly like Von Neumann said it had to be».

Von Neumann even went so far as to explain the way evolution could take place as the machines reproduced. An increase in complexity may come about, he said, when an automaton's blueprint undergoes a change of some kind. Let us imagine, for example, an automaton which bumps into a rigid axle floating next to it in the sea of pieces. If the axle strikes the automaton at the right spot, the collision could change part of the blueprint. And then, when there arrives the moment of reproduction, instead of an exact copy the automaton will give birth to a modified version of itself. A mutation will have been produced and, in this way, fairly primitive automata –equivalent, say, to the complexity of an amoeba– can give rise over time to other relatively complex entities, such as man. Artificial automata can develop in the same way as natural automata, that is, just as animals have developed. Complexity is the decisive factor. Below a certain minimum complexity, the automata degenerated until becoming simple mechanisms, but above that threshold, he claims, «the phenomenon of synthesis, if properly prepared, can become explosive». A veritable race of metal men could be produced whose origin lay in a collection of nuts, bolts and other pieces jostling each other in a primordial sea of automata. John Von Neumann, the Charles Darwin of robots.

Von Neumann's analysis of tridimensional «cinematic», that is, mobile, automata was far from the last word on automata theory. It was, in fact, only the beginning. Stanislaw Ulam, Von Neumann's high school classmate and later colleague at Los Alamos, once suggested that Johnny should investigate a bidimensional, chessboard-like framework for abstract automata. Ulam had made use of a similar system of granular or «cellular» spaces to study crystal growth, and Von Neumann later investigated whether a cellular space of indefinite size might be appropriate for self-reproducing cellular automata. While responding in the affirmative to this question, Von Neumann created an entire new branch of mathematics, «the theory of cellular automata.»

Still and all, as Gödel has shown, mathematics is far from being an exact science. As is probability, or stochastic knowledge. True, it has offered medicine unprecedented prospects in its pursuit of statistical correlations. But as a mathematics professor

humorously told me, a correlation has been demonstrated between conserving one's hair at the age of 70 and the absence of degenerative diseases. Or living in a first floor apartment and suffering aphasia. Correlations sometimes turn up discoveries worthy of humorists [5].

Nevertheless, computers are already creating artificial life. Here in Bilbao, at this very same University, Professors A. Moreno Bergareche and J. Fernández Ostolaza are working on the fascinating subject of artificial life through the computer.

I have chosen to speak of new mathematics and the genome in order to indicate perspectives worth investigating and which are in fact being pursued. But that does not exhaust science's dialogue with the dialectic, with the law, with ethics, mathematics, information sciences, or what is known as artificial intelligence. There are many other horizons. Because the law, in turn, has a direct connection with language. All law is language, Ross might have said.

Please allow me a minor excursus on language and collective or singular personality, parallel to personalism.

Let me begin with a hardly questionable assertion: chemistry did not begin to be a modern science in the current sense until Berzelius endowed it with a universal language still subject, like all language, to a process of degeneration, which is worth noting even though only tangentially.

For biology, language and law are expressed in two systems, analogically and digitally, but with different densities or spheres, and, moreover, involve complex structures, mobile systems and gradual levels of knowledge.

In addition, all these fields involve three different and clearly discernible levels of knowledge: facts, their explanation and the analysis of the procedures and logic that form part of the scientific explanation. Nevertheless, it is necessary to pass on to a fourth level that embraces aspects of the second and third in order to attain greater knowledge. For example: analyzing the predisposition of scientists may be salient to the problem of evaluating scientific theories. Analysis of the significance of the components may be important for delimiting scientific investigation from other kinds of investigation: a term may be used incorrectly, and correctly in another scientific field. In this case there may some-

[5] See Ian Hacking: *La domesticación del azar*, Gedisa, Madrid, 1991, on inferences between databases and what he has called the «probabilistic revolution».

times arise the phenomenon of «absolute simultaneity» (described by John Logee). We might in the same way establish a curious parallel between fecund errors and printing errors (hysterical for historical, for example) and genetic abnormalities.

This is the reason why no system admits the imposition of an external logic, but only the development of a logic internal to its purposes.

Etymologies are not only surprising but also freighted with valuative significance in their space and time: «bravo» derives from *pravus* (evil), the English «silly» from *selig* (holy), and «cretin» from *christianus*, which when introduced in Russia came to mean «peasant». The word «nice» comes from the French *niais* (foolish) which in turn derived from the Latin *nescius* (ignorant), and the different meaning of *mariscal* or *condestable* in French and Italian gave rise to a famously amusing film anecdote.

As with language, slang or jargon, the law knows of customs *sontra legem* or *praeter legem* and physiology of cellular disorders. In legal and biochemical language there are degenerative diseases not caused by something detectable from without but by the internal perversion of a byproduct. At the bottom there is always a norm, a syntax, which is nothing but structure, or as Trench said: «Grammar is the logic of speech even as logic is the grammar of reason».

Each language is a mark of personality: a Spaniard «gives a walk», a Frenchmen «does a walk», and an Englishman «takes a walk». A Frenchman makes attention, while an Englishmen has people pay attention. English objectivity is evidenced in time. I do not have years, I am *X* years old. And even so it leads into illogical pitfalls: a child of one is one year *old*. And to speak only of law, note that «responsibility» cannot be translated into Spanish as *responsabilidad*, the English translation equivalent of which is «liability».

What is more, in the three branches of science, taken as a point of reference, there are losses of meaning: in semantics above all in names and in place-names. La Mancha is dry land, America in Chinese means beautiful land (Mei Kuo), Tel Aviv is Spring mountain, Curaçao is cure, Montenegro is only a translation of the Serb *Corne Gora* or of the Turk *Cornegor*, and Bosphorus means the same in Greek as Oxford in English; Valachian is the land of horsemen and Belize received its name from the pirate Wallace.

Likewise with personal names: Gorky means bitter, Tolstoy fat, Columbus is dove, Machiavelli evil stains.

Words also change their meaning (as occurs with the basic categories of law): pretty originally meant cunning, host and hostile derive from the same root, and the Spanish *espantoso*, dreadful or horrid, means extraordinary in Portuguese.

Yet in these three aspects (biochemistry, language, law), language is not only the word, nor how the how explains the why. When we say the discoveries imply a genuine revolution in medicine, we are making a true assertion. But the greatest part of the path is still before us. And it is certainly honest to recognize in the limits of knowledge certain parallels with now reviled bygone knowledge. Doesn't the affirmation that aspirin blocks erythropoiesis have something in common with or parallel to the sleep-inducing action of sleeping pills? Nobody knows why for sure. Or why certain chromosome triplets cause a degenerative disease.

This relational union of sciences manifests itself in the cause effect crisis which physics was perhaps the first to detect. I remember having read many years ago that the North American psychologist William James had made a similar assertion with respect to the joy laughter or crying sadness relation. Brain biologists today speak of self-induced biofeedback as a solution to many everyday physiological problems affecting all persons. I get the sense that something similar occurs in the structure of the genome and of the law, however distant they may appear in terms of scientific knowledge.

A new theory, if it is valid, would eventually influence legal doctrine and hence case law, and thus end up being reflected in positive law, its origins sometimes dropping from view in the process. With the genome, we know what it is, and sometimes how it acts, but not why. To be specific, why, for example, does the same genetic defect develop into a disease in some cases but not in others, in apparent violation of etiological determinism? Let us not forget that etiology is the search for the *aitia* of the cause itself.

Irrespective of the outer casing –tall or short, thin or fat, old or young– the genome points to what is permanent, to that which remains after the secondary is stripped away. Something similar occurs in linguistics and law. It is not in the words –etymology– where family relationships are found, but in the system (syntax before lexicon) where such relations and linguistic and legal families are to be found. Or put differently: genome investigation bears similarities with linguistic and legal investigation. And it was in the linguistics of this century, although prior to the second half which is the era of genetic investigation, when the differentiation of *syntagma*, *noema* and *lexema* occurred. And there is a common norm –Ausgleich– and a singularity –Spaltung– as relative in their

definition as are the norms of the «standard» human genome. It may rightly be asked whether such a standard really exists or, as I believe, if it is an intellectual statistical creation, something unreal. There is an old saying which goes: «You may paint a tiger, but you will only paint its skin, not its bones».

Man has lengthened the dimensions of his knowledge, widened the frequencies of the visible and the audible, of smell, touch, but today he is aware (relatively) that perceivable reality depends on the instruments which he himself creates. This broadens the synergy of frontier knowledge and science's relativizing synthesis.

It is emergent science which provokes the crisis of society, the awareness that what came before is no longer adequate which makes the foundations of society creak. But what this science –in this case genome genetics *(sit venia verbo)*– poses, together with unexpected solutions to genetic diseases and unimagined vistas to all medical science, is a heartening hour of a hopeful life. Where new knowledge does not clash with beliefs or touch of storms of existential anguish. It is not a matter of suppressing fundamentalisms but rather of overcoming and integrating them, which frustrates the *bonum vivere* of the classics (to which I recommend we return for they are surprisingly close to us) and harvests the greater part of philosophy –of science, of law, and of values– of the misadventurously named post-modernity [6].

In law, genome science enters with new questions, ranging from free will as a foundation of law itself (legal action–reaction) to personal privacy, with commercial, labour, and employment implications, and the legitimacy of certain forms of genetic engineering. These are fundamental issues, which law –or classical jurisprudence– is already accustomed to accepting as givens. The history of law, as a system and as a science, in a certain very peculiar sense is an incessant posing of ethical and social challenges by the sciences conventionally called natural and by political and economic science. All assimilated by the law, in an undefinable sequence of challenges and responses. These responses have undergone the same process as science, discarding those solutions which prove ineffective, artificial or sterile, or ultimately incongruous with the social context in which law is installed as a conventional solution. While true there is a considerable inertial resistance in the law, this is more true for its component categories, sometimes considered as the unmovable pieces of the legal edifice, than for the system's general foundations. As was insightfully observed by Chesterton, what is essential dwells in the small valleys, not in the towering peaks. It is in the minor details where we can see

[6] Roseman, Pauline Marie: *Post-modernism and The Social Sciences, Insights, Inroads and Intrusions*, Princeton University Press, 1992.

how well something is suited to its purposes. We are all capable of major decisions, but few can bear the countless minor inconveniences which nourish life in society.

Perhaps the time has finally come to reconsider not the great foundations of law, but the whole of those legal categories, in order to address the new, unprecedented questions before us. True, the legal system has what Pascal termed *souplesse d'esprit.* And if not, let us find out what is meant by, say, patent and the significance it has had in language and in law. This ability to dissociate referent-referred or ultimate significance is inherent to law and its categories, which incorporates the techniques of semiotics along the trail blazed by Morris and Pierce.

And I am sure that even as ethical considerations of the genome gave rise to a fruitful encounter, so too will this workshop which brings jurists face to face with genome knowledge.

We jurists know much about scorn for basic science. It has been experienced by those of us who began with the basics later to pass on to the legal experience. What was initially scorned has become material and, paradoxically, been converted into a kind of legal fundamentalism, something indisputable, when it was initially scorned and then later disputed. That material has finally been transformed –and the word transform was never better used– into something basic and substantial. Examples to this effect are plentiful among those of us involved in the administrative branch of law.

In the entire treasure chest of knowledge which we conventionally call science, it is important to distinguish from the outset between knowledge from without and knowledge from within the human being. It is in the former where the superiority of man and the abysm separating him from other species can be most clearly seen. Scientific knowledge contemplates man observing him from without as if the observer had nothing to do with the affair. Law, on the other hand, as I will perhaps succeed in making clear further ahead, contemplates man in community with others, that is, from within, conventionally to obtain a level of wellbeing (or if one prefers, an absence of ills and losses of individual liberty provoked by others), but from within. This distinction is of pivotal importance for clarifying the impact of science on law, in such issues as free will, the possible presence of determinism in law, which would eliminate criminal law, and, in general, all conventions (which are nothing but that, pure conventions) of what is necessary within ethics. Reality has become a mere game of itself. There is only artificial reality or hyper-reality.

Sciences, in turn, split or may be conventionally split into pure knowledge –cognizant sciences– or practical knowledge for specific purposes: therapeutic, diagnostic, specific treatments, etc. One and other are separated by a razor's edge, for the latter's existence would be unlikely without the former. Although it does in fact exist, hence my conscious use of the term unlikely and not impossible. All medical science, from Galen or Hippocrates or Paracelsus or Vasalio, parts from empirical observation, not from basic science. Not to mention oriental medicine, based merely on *in corpore nobile* experiences of the tortures of prisoners condemned to death, or the possibility of voluntary biofeedback. Very different, as can be seen, from basic science in the west. Referring always to Europe, true, to such a degree that we judge all other cultures as «ex-European», with an egocentric outlook that time has patiently debunked. In the cultural realm, perhaps because scientists, and doctors in particular, are still swinging back and forth between smiles and a priori dismissals. New genome knowledge brings with it a tug-of-war between what has been ancestrally accepted and the new prospects. Xenophobia is now explicable as something irrational, illicit, counter to the very nature of things. Cross-fertilization implies a genetic improvement, or perhaps worsening, as the case may have it, but something scientifically superior to endogamy.

Jeremy E. Bishop and Michael Waldholz's book tells the story of the most amazing scientific story of our time: the attempt to draw the genetic map of the human body, to locate within the intricate genome sequences those abnormalities responsible for deadly dysfunctions. There are more than 3,000 genetic diseases which have resisted the efforts of traditional medicine, because the cause comes not from without but from within the person. And the very paradox that viruses –which the World Health Organization says account for one third of all visits to the doctor and which the recent Nobel Prize winner Lederberg has classified as man's only real competitors for mastery of the planet– are the vectors of genetic manipulation for therapeutic purposes. For the evil or truth of everything that exists is relative, and this is true not only in medicine.

In all the questions we put to law or the legal system, we must be aware that we will only obtain answers which are slanted (from the standpoint of the questioner) and relative. The first adjective seems clear. The second needs some refinement. If we ask what is glucose, the answer will be –should be– different according to the context in which the question is asked. If a chemistry professor asks his student, the correct answer would presumably be its chemical formula. The answer would be different if the question is asked of a diabetic patient by his doctor, or of a child by his elementary school teacher.

The relativity of questions manifests itself in the most obvious of areas: in arithmetic.

A popular scientific writer recently gave the following example of this assertion:

«Suppose we say 2 + 2 = an integer. The answer would be correct, wouldn't it? Or suppose we say 2 + 2 = an even integer. It would be even more correct.

If the teacher wants them to give 4 as an answer, and does not wish to distinguish between the different incorrect answers, wouldn't this suppose unnecessary limits on comprehension? Suppose the question is how much is 9 + 5 and the student answers 2? Wouldn't he be ridiculed and told the right answer is 9 + 5 = 14? If he is then told that 9 hours have passed since midnight and that it is therefore 9 o'clock, and he is asked what time will it be in 5 hours, the student answers saying 14 o'clock, because 9 + 15 = 14, won't he be criticized and told that its two o'clock?. Apparently, in this case the correct answer is 9 + 5 = 2.

Or suppose once again that the student says 2 + 2 = 11 but before the teacher can send him home with a note for his parents the student adds:

– In base 3 of course.

The student would be right. Here is another example. The teacher asks who was the 40th president of the United States? The student replies, there was none, teacher.

– Wrong, says the teacher. Reagan was the 40th president.

– No way, says the student. I have here a list of all the persons who have been president of the United States according to the Constitution since Washington to Reagan, and there are only 39, therefore 40th president does not exist.

– Ah, replies the teacher, but Grover Cleveland served two non-consecutive terms. The first from 1885 to 1889 and the second from 1893 to 1897. He was the 21st and 24th president. So Reagan is the 39th person to hold the presidency and at the same time the 40th president.»

Science advances by relativizing its results. It has been said that we live in Newton's physics, with Einstein's relativity but with the morality of Frankenstein. Because the advances of science are relative, unidimensional and not progressive in their entirety. And

we must recognize these facts if we wish to have a proper starting point.

When someone asks whether we're home alone and we answer that, yes, we are alone, we do not mean to say that the doorman or maid or our family aren't there, because what we really want to say is that there is no visit or that our time is free.

As can be seen in this and many other examples, the quality and context of the question, shapes the answer in a conventional way which no researcher (biochemist, linguist or jurist) should forget or ignore, save at the risk of absolutizing the answers and hence rendering them meaningless.

As an introduction to the subject and its legal aspects there is perhaps no better place to start than the definitions set down by the European Parliament.

As early as March 16th 1989 the European Parliament adopted a resolution on the legal and ethical problems of genetic manipulation (*OJ* [*Official Journal of the European Communities*] 96, April 17th 1989, p. 165).

Regulation of these areas within the EEC began with the Council recommendation on registering work in which recombinant DNA is used (*OJ* 231, July 21st 1982, p. 15), followed by the proposal for a Council directive on international release into the environment of genetically modified organisms (Document COM 88, 160, December 14th 1988). There also exists the 1988 proposed directive on the liberalization of genetically modified organisms, and the Council Decision of June 26th 1990 adopting a specific technological research and development programme in the specific field of health and insofar as concerns the human genome.

The European Parliament has an international commission charged with evaluating the evolution of human genome research and genetic engineering. Many countries have their own such national commissions.

Notwithstanding their parting principle of freedom of scientific investigation, all these documents underscore human dignity as a limit to such investigation. Scientific progress is to be not detained but legally regulated.

According to the European Parliament, genetic investigation must meet the following requirements:

a) Such research shall have as its sole purpose the wellbeing of the interested parties and be based on the free decision of

the same, who, if they so request, shall be notified as to the results.

b) Genetic analysis shall not be used for purposes of negative selection of genetically undesirable traits or to establish genetic standards (eugenesia). A recommendation by the Assembly of the Council of Europe indicates that: «The rights to life and to human dignity, which are protected by articles 2 and 3 of the European Convention on Human Rights, imply the right to inherit a genetic pattern which has not been genetically modified in an artificial way».

This decisive conclusion has been called into question and is now open to debate insofar as it implies a prohibition of genetic enhancement of offspring, particularly from the negative standpoint, the right to not inherit scientifically detected and remediable genetic defects.

c) The principle of the interested party's personal self-determination is superior to any economic considerations of the health-care system. All persons have the inalienable right to know or to not know their genes.

d) Genetic mapping may only be performed by properly trained professionals. The storage and evaluation of genetic data by government or private bodies is prohibited, as such data could be used if risk groups were identified beforehand. The data must therefore be confidential.

e) Genetic strategies must not be promoted as solutions to social problems. Genetic information is not by itself sufficient to determine human characters, which are also affected by external factors such as upbringing, environment and family.

Lastly, the data must be reliable, refer to specific clinical situations, and be of immediate medical use to the interested parties.

f) In February of this year an objection was filed to the patent which the EPO (European Patent Office) had issued to Harvard University's onco-mouse or cancer mouse. The same has occurred more recently with the application filed by the Spanish ICEMA (Resolution 0249/1993).

All this has demarcated the field of genetic knowledge and genetic engineering. But there are other additional questions to address [7].

[7] Cf. Sáenz Gil, Rubén: *Manipulación genética y Parlamento Europeo* [Genetic manipulation and the European Parliament], *EEC News*.

1. Genetic engineering and mapping must aim to improve working conditions and never to discriminate against employees with detected genetic risks.

2. Genetic analyses may only be used with a court order or during judicial proceedings. They are admissible as evidence in paternity suits and criminal proceedings, but are not admissible as the basis for characteristics or behavioral peculiarities.

3. Genetic engineering requires the consent of the interested party and a favourable risk-benefit analysis. This limitation points to the fact that:

   - Transferred genetic material is still uncontrollable as to point of insertion as well as hereditary transmissibility of the correction.

   - Functional disorders may be produced.

   - The retroviruses used as vectors may prove to be oncogenic.

   - The tissue-specificity of the vector retrovirus cannot be guaranteed.

   - The human embryo must be guaranteed protection of its genetic identity. Here the demarcation between identity and pathology is particularly delicate. It is jointly incumbent on scientists and jurists to delimit the potential conflicts.

   - Cloning must be prohibited. All persons have the right to their unique and unrepeatable identity.

   - Production of so-called «chimeras» consists in the fusion in a single embryo of «totipotent» cells from genetically distinct embryos during early cell division. Human dignity seems incompatible with the production of chimeras.

4. The April 10th 1972 agreement on the prohibition of development, production and storage of bacteriological and toxic weapons and on their destruction should be broadened to the potential biological weapons applications of genetic engineering.

5. In view of the proliferation of genetic research centres, the European Parliament has indicated the need for their control and security. Regulations should be set down for the manipulation of pathogenic microorganisms and germs, and for

their classification, by degree of hazard, as well as for the certification of the researchers working with said organisms.

There are two proposed Directives on the need to curb the liberalization of genetically modified organisms until safety rules are set down. Both proposals are from 1988.

6. Lastly, we still do not know the ecological consequences of environmental release of genetically modified organisms, which may eventually destroy natural ecosystems, give rise to new diseases, or transfer to man genetic traits introduced in animals or plants. According to the European Parliament, the safeguarding of life and health demand the adoption of special protective measures.

This is the troubling panorama of legal concerns in the European Community, with respect to preliminary precautions and oversight rules.

Even more important than these rules, which may be regarded as no more than provisional, is to verify and debate the impact of genome knowledge on the legal system.

If the legal system's response to the questions prompted by the human genome does not contribute to solutions, then the law itself is part of the problem and the entire legal system must be reconsidered.

Time, that great devourer of all that exists, also swallows scientific knowledge and, within law, obscures the how and why of its institutions and legal categories. These responded in their day, now remote in most cases, to the challenge response dialectic which is the driving force of life. The search to find those roots contributes in great part to relativizing what is considered by us as axiomatic in the legal system, if it is that such a thing as incontrovertible scientific or social axioms exists. For example, in linguistics it is hard to find the origin of the word *ciao*, so often used by Italians, and its connection with *schiavo*, an expression of courtesy. I personally believe linguistics bears more resemblance to legal structure than we might have initially thought. The linguistic atlases resemble the genome map without ever being as instantaneous and individualized. Exactness requires time, and time is the destroyer of all possibility of definitive maps. Does something similar not occur in law? We might also ask biochemists whether such parallels exist in their science; whether there exists some unknown link between will and genome. The behaviour of genetic abnormalities which in statistics appear as exorbitant in the cause effect connection (etiology pathology), which should inexorably be correlation I, and are not in statistical

terms, poses important problems. The exceptional, the inexplicable and the unrevealed have escaped that stark scrutiny to which science wishes to lead us.

This assertion points to what I said before about the cause effect connection being scientifically questionable in all fields. In my allusions to the relativism of our scientific knowledge, I would like to mention a thought which paradoxically enough was raised by a well-known humorist. When we laugh at the site of backward peoples beating their drums to chase away evil spirits, we do not realize how much they resemble us when we try to get out of a traffic jam by sounding the horn.

The internal connections of the legal edifice can only be tested when one of its non-critical stones, say, imputability, is changed. The current legal system has survived two millennia without internal fractures. It has only replaced, and very subtly, its language and, gradually, its component pieces. These have come to make up a new structure, but leaving the roles of each stone and each institution untouched.

The development and history of the law may be graphically depicted, as internally it obeys a recent entropy, an incessant ingestion of the science, politics, economics, and ethics prevailing at each historical moment. Law has known how to adapt itself to every age. Like semiotics or any other science, law has its anomalies, errata, inertias, borrowings which cannot be returned without being invalidated, its external unintelligibility and incompleteness. The very idea of patent, disease, will, capacity, pain, damages, defect, liability will have different signifiers and significances and referents, depending on the country, person, era and time.

This enhances and testifies to the structural similarity between the three linguistic, legal and biochemical approaches I have highlighted. And in addition to these there is another mathematical perspective, still largely unexplored, which can furnish unprecedented and unfathomed solutions.

Suppose for a moment that we have obtained the entire skeletal structure of the genome and, moreover, that we know the function or purpose or consequences –whichever you prefer– of each combination of the component nucleotides of not just a chromosome but of the whole genome. This still futuristic prospect is similar to that facing jurists to the extent that we know the governing norms –all the civil, commercial, fiscal, administrative, European Community and local norms– that regulate all activities carried on by citizens. Then we –scientists, jurists or biochemists– would know the conditions, in the widest sense, of behaviour

adapted to the rules, optimized or standardized rules, according to what aspect of human action we consider.

I would tell biochemists that a jurist has something to say from this future perspective, because it is already present before us. We know, or can know, the legal conditions of any conduct. This, in short, is the meaning of the legal certainty which article 9 of the Spanish Constitution preaches. But it preaches in a desert.

We may do away with cancer, degenerative diseases and cardiovascular ailments, but until human conduct is changed by moral education, they will be replaced by death from war and violence. This prediction comes not from me but from the WHO in its latest annual report.

Hence the importance of law and ethics, the reason for these colloquiums which bring together such seemingly disparate fields of knowledge.

In conclusion, all jurists begin with the legal case, go on to doctrine and the legal system, and end up with the philosophy of law, to perhaps conclude with the theology of law. This may also be the course followed by biologists. For now I conform myself to having raised questions, paradoxes and perspectives, perhaps obvious ones. To others I will leave the answers, which I am sure will be extremely interesting given the calibre of the participants.

I close all this with an apology for having delivered a talk much closer to Maldenbrot's mosaics than to the rules of Cartesian discourse.

ROOTS OF CONTROVERSY: ORIGINS OF THE HUMAN GENOME PROJECT

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The Human Genome Project was born of technological innovation. It started as the independent ideas of three individuals to derive a sequence of DNA in the human chromosomes, and then became a concerted program to produce three kinds of genetic maps. In 1984 and 1985, Robert Sinsheimer and Renato Dulbecco came upon the idea of sequencing the human genome. They reached the same conclusion via quite different routes, linked only by proximity in time and residence in California. Late in 1985, Charles DeLisi, working for the Department of Energy (DOE), came upon the idea yet a third time, and he was in a position to translate the idea into a government research program. Once the DOE program was launched, rivalry between DOE and the National Institutes of Health (NIH) propelled the genome project to the front pages of *Science*, *Nature*, and major newspapers, and set it on a course toward seemingly perpetual controversy.

The initial idea was to sequence the genome, but this presupposed some prior goals –various genetic maps, including those for organisms whose genetics were better understood and that were more amenable to experiment than humans. The genome project was redefined between 1986 and 1988 to embrace three technical goals. The first among these is a genetic linkage map to enable the tracing of inheritance through human pedigrees. The second

objective is a set of physical maps to facilitate the direct examination of DNA, by producing ordered collections of cloned DNA fragments that can be used to study chromosomal regions. These objectives, mentioned at first as stepping stones to the complete genomic sequence, in the view of some will ultimately prove to have been more useful to complete than the original primary goal of comprehensive sequencing information. The third kind of map, most closely related to the conceptual origins of the project, is DNA sequence information sufficient to expedite the study of genes and other features of interest.

It was clear from the outset that to attain these technical goals, the genome project needed to acquire resources. The main argument for the genome project rested on an argument about the commons: that a concerted effort to construct tools for human genetics would accelerate medical research and reduce its ultimate cost; a shared resource was more valuable than disparate and uncoordinated efforts. In this sense, the genome project was a road-building project for genetics, itself coming to take center stage in biomedical research. The underlying premise was that genetics was becoming a fast track to find cures, means of prevention, and better treatments for many diseases. Building an infrastructure to support this effort, by constructing maps systematically, would benefit all research. This rationale built upon the arguments for biomedical research pursued so successfully since World War II, resting on the value of research to combat disease and relieve suffering. The genome project's two distinctive features were that (1) it was aimed not at a particular disease, but explicitly promised to make research on many disorders faster and less costly, and (2) the idea came not from a disease-oriented advocacy group but from the scientific community. This testified to the enlarging scale of the biomedical research enterprise, now sufficiently large to merit its own infrastructure project and sufficiently powerful to secure funding for it.

In addition to the disease rationale, the genome project promised to foster technology development. Technology development became a process goal in addition to the mapping goals. Technological innovation was necessary to attain the mapping goals at a reasonable cost and in a reasonable time. Once embraced, however, technology development took on a life of its own, now centered in technology policy, rather than science policy. In this case, the distinction had bite.

Technology development became inevitably linked to technology transfer, and hence to intellectual property protection. While science might adhere to international norms –with its ideals of data sharing, relentless pursuit of truth, and a single international standard of excellence– technology policy found a more natural

home among nationalistic economic aspirations. The genome project was presented to policy-makers as, in part, a road to economic competitiveness in biotechnology. This rationale can be found in debates that led to genome projects in the United States, United Kingdom, Italy, Japan, the former Soviet Union (and subsequently, Russia), the European Community, France, and Canada.

The attempt to straddle the fence between science and technology led directly to conflict between the mapping goals and technology transfer goals. Map information is useful only to the extent that it is comprehensive and widely available. Maps save effort only if their information is accurate, complete, and freely shared, so the construction process need not be repeated. Efficiency derives not only from economies of scale and technological innovation, but also from avoiding unnecessary work. But if the process of map construction is proprietary, held to be a national endeavor whose economic fruits are to be picked locally, then sharing data endangers the national interest until the intellectual property has been locked up. At the level of international science policy, this presents a true prisoner's dilemma: all countries are better off if all information is shared, but each country has domestic proprietary interests that can endanger cooperation.

Some have argued that patents are not problematic, because data can be shared as soon as patents are filed. One need not hold the information as a secret once a patent application is filed. While it is true that patents do not necessarily hinder data-sharing after patent applications are filed, the dilemma remains because each nation retains an incentive to try to stake its claim early, lest it sacrifice its economic interest. When the American West was opened in the mid-1800s, one of the major forces was a quest for gold. Gold rushes repeatedly washed across middle America toward the Rockies and California. Each person could file only limited land claims for mineral rights on the land staked, and no claim was to be awarded unless a mineral value was proven. This did not stop the gold rushes [1].

[1] John Wesley Powell, who ultimately headed the first mission-oriented science agency in the US Federal Government, was wise enough to see immediately that the true constraining resource in the American West was water, and access to it the key to development. He urged policies to allocate access rationally, but this flew in the face of the prevailing ideology and, more importantly, the mining, ranching, farming, and railroad interests already becoming a major presence. He was ultimately deposed as head of the US Geological Survey by Senator William Stewart, a Western Senator. Wallace Stegner described Stewart in *Beyond the Hundredth Meridian:* «Robust, aggressive, contentious, narrow, self-made, impatient of "theorists", irritated by abstract principles, a Nevada lawyer, miner, Indian-killer; a fixer, a getter-done, an indefatigable manipulator around the whiskey and cigars, a dragon whose cave was the smoke-filled room, Big Bill Stewart was one to delight a caricaturist and depress a patriot... He believed in Western "development", and he believed in the right of men –himself among them– to get rich by this "deve-

The parallel to genome research is unmistakable. Each nation has an incentive to invest its resources so as to secure a strong patent position in an international competition. The only way to do this is to direct a research strategy to lock up gene patents first –a gold rush for intellectual property rather than mining claims. The danger is not only international friction, but waste, fomenting the kind of duplication now occurring with some crop plants, where independent groups are independently constructing maps, but most likely only the first group to complete such a map will reap the full rewards of intellectual property protection. To the extent that these efforts are paid by taxpayers in the various countries involved, only those residing in the winning country will have made the wise investment. There are political stakes in losing, and thus political dangers in pursuing a cooperative strategy, despite the obvious waste of overall resources.

The historical parallel is not complete, however. Those pursuing the claims are not poor and struggling prospectors, but developed nations with broader interests and strong scientific traditions. Moreover, they are relatively few in number and have an opportunity to craft international agreements to accommodate disparate policy goals held in metastable tension –a desire for international sharing of valuable genetic data of benefit to all and national interests in economic competitiveness. And the territory to be claimed is vast and relatively unexplored. Unless patent law is a less flexible instrument than it has proved to be in the past, there should be treasures to be found for many decades, no matter who first draws the maps or puts tollgates across the trail heads. If initial claims are too broad, we can be confident that clever lawyers will endeavor to obliterate them; if early patents become obstacles to important social goals, including commerce and pursuit of knowledge, then courts will find a way to maneuver around them.

Concern for how the information resulting from gene mapping would be used, and how the tools of genetic technology would be employed, led to a second major process goal in addition to technology development –an inspection of the ethical, legal, and social implications of genome research. Pursuit of this objective

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lopment".» Powell's fate in 1894 suggests a tantalizing parallel to the fate of Dr Watson. In an ironic twist, I sent the pages from Stegner's biography of Powell to Watson early in 1988, when rumors first floated that he might head up the NIH genome program. Watson's response (in a gentle paraphrase): «I know Washington's a dangerous place. I'll need help». «By a twist of fate, Dr Watson was similarly out down by political intrigue, when he came a cropper at the hand of NIH Director Bernadine Healy. The focus of contention-gene patents. He resigned as director of the NIH genome center in 1992. Where Powell identified water as the West's critical scarce resource, Watson recognized genes as the precious commodities buried in the genetic wilderness».

spawned a research program to anticipate the harmful uses of genetic information, to ameliorate these adverse impacts, and to promote beneficial applications. This program on the ethical, social, legal, and economic aspects of genome research was unprecedented in major scientific or technical projects, but caught hold in every country and organization that crafted a genome project save the United Kingdom. This movement toward social responsibility was read by some as a cynical ploy to buy off the critics, or as a preemptive strike to protect the soft historical underbelly of human genetics –its association with eugenics and racial hygiene.

The chequered history of American and British eugenics and Nazi racial hygiene haunted even the earliest public discussions of the genome project. Concerns about misuse of genetic testing and disregard of private genetic data surfaced as the project was first discussed among Members of Congress and their staffs. While Dr Watson did not confer with his superiors before announcing his intention to set aside a fraction of the budget for «ethics», he did follow the lead of the two 1988 policy reports that attended the birth of the genome project in the United States –one by the National Research Council and the other by the Office of Technology Assessment. These reports, and their analogs in other countries, recognized the special sensitivities surrounding genetic data about ourselves, and noted the importance of explicit attention to the potential for genetic discrimination, breaches of privacy, stigmatization, and other harmful effects of genetic information. Establishing a research program to pursue these issues was a logical step, remarkable less because it was taken than because no other program had taken it before.

A decade and a half earlier, the biomedical research community confronted the unknown public health effects of recombinant DNA research. The transient self-imposed moratorium and vigorous debate both inside and outside science signaled a recognition that biology, and specifically molecular genetics, had consequences beyond its borders. The debate about the wisdom of that moratorium is still quite active, and there are heartfelt criticisms on both sides still, but it is nonetheless clear that the debate was about scientists' social responsibilities. The establishment of an ELSI research program for the US genome effort, or more precisely two separate but coordinated programs under DOE and NIH, was a different response to a similar problem. Rather than a moratorium to eliminate a potential public health risk (of unknown magnitude), the policy was to mount a parallel effort to ferret out the consequences of scientific progress and technical application, initiated before much of the new knowledge was discovered and before the new technologies and their applications became routinely available outside scientific laboratories. The dif-

ferent response is in part due to the different nature of the risks. Recombinant DNA was feared to be a means to produce novel contagion with immediate health consequences; the risks associated with genetic information were (in general, although not in every case) less immediate, and the harms more social than medical.

The birth of ELSI programs may be unique to human genetics, or perhaps it is an artifact of a broader renegotiation of the social contract supporting research in all fields, or at least all biomedical research. The fact that the trend caught on in so many countries suggests that the same trend prevailed world-wide, not just in North America, Europe, or Asia. Because all the programs were started around the same time, and because all were focused on genome research, we cannot yet tell if other, different research programs will be similarly expected to address their social impacts. It could turn out that the genome project was merely new in the late 1980s and early 1990s, and became but the first example, with others soon to follow. It is certainly plausible that information science, nuclear fusion, energy research, and many other fields have as many ethical, social, and legal impacts that could be similarly addressed. Or the genome project may remain unique in attending to its social and ethical ramifications.

Whether the Genome Project remains alone or is joined by other ELSI programs in other areas, I believe that the existing research program in the United States, at least, is incomplete. If this is a grand policy experiment, it is missing an ingredient. The purpose of the US program was not only to pursue knowledge about the uses and abuses of genetic information, which its infusion of cash and program direction has certainly succeeded in doing, but to formulate policy options to promote benefits and forestall harms. The US program has, to date, issued two policy statements, one on implementation of a US law to prevent discrimination against the disabled and the other on pilot testing of screening programs for cystic fibrosis (CF) mutations.

The ELSI Working Group's statement on the anti-discrimination law, the Americans with Disabilities Act of 1989, had no appreciable impact. This does not mean it was not worth doing, but that it did not succeed. The second statement, on pilot testing of CF screening, led to a new research program that will almost certainly improve national policy. This program would almost certainly not have been started as early but for the intervention associated with the genome project, and so this policy intervention can be considered a success. The difference may be that the CF pilot testing program was within the province of NIH, while implementing the Americans with Disabilities Act was handled by a separate part of the bureaucracy. These two ELSI Working

Group policy initiatives are important and should not be discounted, but given the magnitude of the research program and the widespread recognition that there are serious policy questions to address, these two brief statements do seem slim pickings.

This criticism is not intended as finger-pointing. I am among those fingered, as a member of the ELSI working group that advises NIH and DOE. Rather, I merely point out that there is an important gap to fill. The US program has struggled since its inception to discover a way to do more in the policy realm. The intricacies of bureaucracy have thwarted a bolder approach, and the inherent drive to support more research with its academic constituency, rather than to pursue serious policy analysis with its less certain outcome and more fractious constituency, has not led to a solution. It may be that the solution is beyond the control of the Genome Project itself, and will require direct intervention from Congress or high up in the executive branch.

Across the Atlantic, in the United States, there is much talk again of a national bioethics commission or an ethics advisory board to help guide biomedical research. Several models have been proposed, and one or more of these might serve to plug the gap, or at least attempt to do so. The US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research functioned successfully from 1974-1978. The Ethics Advisory Board operated from 1978-1980. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, the most recent and perhaps the best known US bioethics commission, existed from 1980-1983. These were all successful models of policy analysis. The news is not all good. Several more recent experiences suggest tempered optimism may be prudent.

Several attempts to deal with bioethics at the national level failed in the late 1980s. The Biomedical Ethics Advisory Committee, a commission answering to a congressional board, died in 1989, caught in a political crossfire over the question of abortion. Two other efforts to deal with matters of biomedical research and ethics also failed during this period. An NIH panel that considered transplantation of fetal tissues made recommendations that were pushed aside, and an attempt to re-establish an Ethics Advisory Board also fell short. It is possible that American politics have permanently poisoned the well, making a national forum impractical. I am an optimist, however, and believe that we will find a way to sustain rigorous analysis of national policy issues raised by genome research.

Over the next several days, we face a task even more daunting in some ways than that facing a national bioethics group. We

hope in a single meeting to address some of the legal challenges posed by genome research. We come from diverse cultural backgrounds, legal systems, and technical disciplines. Many regard international meetings as occasions for political posturing, endless rhetoric devoid of substance, and vacuous generalization. We will doubtless indulge in some or all of these; indeed I already have. Yet there are grounds for optimism even here. We can all agree that there is only one science, adhering to an international standard. We can also point to occasional successes in international law.

One of the striking features of the post World War II era is that international standards of behavior have changed. During the Irish potato famine, Ireland also had bumper crops of corn. There was not so much as a whimper from the international community as the corn was sold for export while the Irish died by the thousands. After World War II, the nations of the world came together to draft some statements about international human rights. These have become the foundation of a vigorous international movement that has had an impact. Its accomplishments may be incremental, a signal difficult to detect above the considerable noise of political ferment, but the trend is obvious. The former Yugoslavia demonstrates the potential for bestiality of the first order despite the new canons of behavior, but there is a definite difference from the period before World War II –we all know it is happening and have not remained silent. Action may not follow from the screams, but at least the screams are loud and persistent, and who knows, they may ultimately make a difference.

It is also prudent to be humble and expect change to take a long time, but we do not have to be sentimental or naive to believe we can achieve progress through international law.

CHRONOLOGY OF THE HUMAN GENOME PROJECT
emphasizing 1985 until its «official» beginning in October 1990
(Items in italics are major precursor events)

Date	Event	People or Group	Place or Institution
April 1978	*Idea for systematic approach to human genetic linkage map*	*David Botstein and Ronald Davis*	*Alta, Utah*
April 1981	*Project to automate DNA sequencing begins*	*Akiyoshi Wada and colleagues*	*Science and Technology Agency, Japan*
June 1984	*Polymerase chain reaction idea presented at poster session*	*Kary Mullis at Cetus Corporation's scientific retreat*	*Monterey, California*
November 1984	*Center for the Study of Human Polymorphisms forms an international collaboration*	*Jean Dausset and others*	*Paris*
December 1984	*Meeting on technologies for direct DNA analysis of the human genome to detect mutations*	*DOE conference*	*Alta, Utah*
May 1985	**Meeting on sequencing the human genome**	**University of California, Santa Cruz**	**Santa Cruz, California**
October 1985	**Italian Embassy meeting where Dulbecco introduces idea of sequencing the human genome**	**Renato Dulbecco**	**Washington, DC**
October-December 1985	**Beginnings of Department of Energy plans for a genome project**	**Charles DeLisi with David Smith and others**	**Germantown, Maryland**
February 1986	Trustees discuss genetics databases and genome project idea	Howard Hughes Medical Institute	Coconut Grove, Florida
February 1986	**First letter to Commission of the European Communities**	**Sydney Brenner**	**Brussels, Belgium**
March 1986	**First Los Alamos meeting on sequencing the human genome**	**DOE conference**	**Santa Fe, New Mexico**
March 1986	***Science* commentary on sequencing the human genome**	**Renato Dulbecco**	***Science***
May 1986	DOE planning memo outlining genome initiative	Charles DeLisi	Germantown, Maryland
June 1986	Automated fluorescent DNA sequenator prototype announced	Lloyd Smith and others in Leroy Hood's group	California Institute of Technology, published in *Nature* and also announced at Cold Spring Harbor Laboratory

Date	Event	People or Group	Place or Institution
June 1986	Polymerase chain reaction described at Cold Spring Harbor meeting	Kary Mullis from Cetus Corporation	Cold Spring Harbor Laboratory
June 1986	**Session on genome project at meeting on the Molecular Biology of *Homo sapiens***	**Paul Berg and Walter Gilbert, cochairs**	**Cold Spring Harbor Laboratory**
July 1986	**Informational Forum on the Human Genome**	**Howard Hughes Medical Institute**	**National Institutes of Health**
July 1986	DOE plans presented to Office of Management and Budget, approval for $4.5 million reprogramming	Charles DeLisi presents to Judith Bostock and Thomas Palmieri	New Executive Office Building, Washington, DC
August 1986	Board on Basic Biology and Commission on Life Sciences meeting on genome initiatives	National Academy of Sciences	Woods Hole, Massachusetts
September 1986	**National Research Council study approved**	**Governing Board Executive Committee, National Academy of Sciences**	Washington, DC
September 1986	**Office of Technology Assessment project approved**	**Technology Assessment Board, US Congress**	**Washington, DC**
October 1986	Publication of papers demonstrating approach to physical maps of yeast and *C. elegans* in *Proceedings of the National Academy of Sciences*	Maynard Olson and colleagues (yeast); Alan Coulson, John Sulston and colleagues *(C. elegans)*	Washington University, Saint Louis (yeast); MRC Molecular Biology Laboratory, Cambridge *(C. elegans)*
October 1986	**54th meeting of the Advisory Committee to the Director, National Institutes of Health**	**NIH Director's office convenes public meeting**	**National Institutes of Health**
December 1986	Office of Management and Budget review of DOE genome initiative, first move towards line-item budget	Charles DeLisi and Judith Bostock	Washington, DC
January 1987	Second Los Alamos meeting, on automation and robotics in DNA analysis	DOE conference	Santa Fe, New Mexico
February 1987	Costs of genome project projected for DOE	Human Genome Subcommittee, Health and Environmental Research Advisory Committee, DOE	Denver, Colorado
February-March 1987	**Appropriation hearings for NIH result in first earmarked genome budget for fiscal year 1988**	**House and Senate Appropriations Committees**	**US Congress**
March 1987	**Hearing before DOE authorization committee, US House of Representatives.**	**Lee Hood, Charles DeLisi, Eileen Lee and congressional staff**	**US House of Representatives**

Date	Event	People or Group	Place or Institution
March 1987	NRC Committee discusses genome program budget	National Academy of Sciences	Washington, DC
March 1987	Hearing before House Select Committee on Aging	Rep. Claude Pepper, on National Library of Medicine plans for a National Center for Biotechnology Information	US House of Representatives
March 1987	Meeting to join DNA sequencing project to human genome project	Science and Technology Agency	Tokyo
April 1987	Health and Environmental Advisory Committee report on Human Genome Initiative	Outside advisors to DOE	Washington, DC
May 1987	**Italian genome program begins**	**Renato Dulbecco, Paolo Vezzoni and others**	**Rome**
May 1987	**Meeting with House and Senate Appropriations Committee Members and Staff on AIDS and Human Genome**	**James Watson, David Baltimore and Bradie Metheny on behalf of the Delegation for Basic Biomedical Research**	**US Capitol**
May 1987	**Senator Domenici holds meeting on the future of DOE's national laboratories**	**Senator Pete Domenici, Donald Fredrickson, Jack McConnell, congressional staff, and others**	**US Capitol**
June 1987	OTA workshop on collaboration and intellectual property	Office of Technology Assessment	US Congress
June-July 1987	Senator Domenici moves to tack a genome provision onto international trade bill	Senator Pete Domenici	US Senate
August 1987	OTA workshop on costs of genome project	Office of Technology Assessment	US Congress
August 1987	Workshop on genome project	Senator Pete Domenici and staff	Santa Fe, New Mexico
September 1987	Hearings on DOE and NIH genome programs	Senate Committee on Energy and Natural Resources, Senators Wendell Ford, Pete Domenici and their staff	US Senate
Fall 1987	**Senate bill 1966**	**Senators Lawton Chiles, Edward Kennedy and Pete Domenici**	**US Senate**
September 1987	First national laboratory genome centers announced	Department of Energy	AAAS meeting, Boston
October 1987	DOE and NIH begin first fiscal year with earmarked genome appropriations (fiscal year 1988)	House and Senate Appropriations Committees	US Congress
October 1987	**Human genetic linkage map published in *Cell***	**Helen Donis-Keller and others**	***Cell***

Date	Event	People or Group	Place or Institution
December 1987	**USSR genome program presented to government officials**	**Alexander Bayev and Andrei Mirzabekov**	**Moscow**
February 1988	**National Research Council report released**	**National Academy of Sciences**	**Washington, DC**
March 1988	Presentation to General Assembly of USSR Academy of Sciences	Alexander Bayev	Moscow
February-March 1988	***Ad Hoc* Advisory Committee on Complex Genomes**	**NIH Director's office invites NRC and OTA committee members and others; James Wyngaarden announces intention to form Office for Human Genome Research at NIH**	**Reston, Virginia**
April 1988	International Conference on Bioethics: Human Genome Sequencing	Economic Summit (G-7) and Italian National Research Council	Rome
April 1988	**Office of Technology Assessment report released**	**Committee on Energy and Commerce, Rep. John Dingell and staff person Lesley Russell**	**US House of Representatives**
April 1988	**Human Genome Organization Founded**	Victor McKusick, Sydney Brenner, James Watson, Leroy Hood and others	**Cold Spring Harbor Laboratory**
May 1988	**First scientific meeting on human genome mapping and sequencing**	**Maynard Olson, Charles Cantor and Richard Roberts, organizers**	**Cold Spring Harbor Laboratory**
June 1988	**Hearings on NIH-DOE collaboration on genome programs**	**Committee on Science and Technology, Reps. James Scheuer and Douglas Walgren and their staffs**	**US House of Representatives**
July 1988	Latin American Network for Biological Sciences passes genome resolution	Jorge Allende and others	Quito, Ecuador
October 1988	James Watson appointed NIH associate director for human genome research	**James Wyngaarden**	**National Institutes of Health**
October 1988	First International Workshop on Collaboration for the Human Genome Project	**Santiago Grisolía and others**	**Valencia, Spain**
December 1988	Letter to Mikhail Gorbachev about the USSR Human Genome Program	Alexander Bayev	Moscow

Date	Event	People or Group	Place or Institution
December 1988	USSR Council of Ministers Approves USSR Human Genome Program	Alexander Bayev and Andrei Mirzabekov	Moscow
January 1989	UNESCO forms Scientific Coordination Committee for the Human Genome	Federico Mayor and UNESCO staff	Paris
February 1989	**Genome program officially begins in the United Kingdom**	**Sydney Brenner, Walter Bodmer, James Cowan and government officials** (Medical Research Council and Imperial Cancer Research Fund)	**London**
April 1989	**Ministry of Education genome program begins**	**Kenichi Matsubara and government officials**	**Tokyo**
June 1989	**Human Genome Analysis Programme approved**	**Commission of the European Communities**	**Brussels, Belgium**
June 1989	Joint meeting of UNESCO, HUGO, and USSR Human Genome Program	Council on International Cooperation on the Human Genome	Moscow
August 1989	**NIH-DOE planning retreat**	**NIH and DOE advisory committees**	**Banbury Center, Cold Spring Harbor Laboratory**
September 1989	Cystic fibrosis gene identified	Francis Collins and others	University of Michigan and collaborating centers
September 1989	**First meeting of NIH Working Group on Ethical, Legal, and Social Issues**	**Nancy Wexler, chair**	**The Cloisters, National Institutes of Health**
October 1989	**NIH Office for Human Genome Research becomes National Center for Human Genome Research, with budget authority**	**Louis Sullivan, Jr, Secretary**	**Department of Health and Human Services**
October 1989	First DNA Sequencing Conference	J. Craig Venter and C. Thomas Caskey, organizers	Wolf Trap Farm Park, Virginia
November 1989	Hearing before Committee on Commerce, Science, and Transportation	Senator Albert Gore, Jr	US Senate
December 1989	DOE joins program on Ethical, Legal and Social Issues	Joint NIH-DOE advisory committee	Wilson Hall, National Institutes of Health

Date	Event	People or Group	Place or Institution
February-August 1990	**Letter and electronic network campaigns opposing genome project**	**Martin Rechsteiner and colleagues; Michael Syvaanen and colleagues**	**Universities and research centers**
February 1990	UNESCO conference on ethical issues	UNESCO and other organizations	Paris
April 1990	**NIH-DOE joint five-year plan**	**NIH and DOE staff**	**Washington, DC**
June and October 1990	**Genome program announced by the Government of France**	**Hubert Curien**	**Paris**
June 1990	Latin American network officially launches genome collaboration	Jorge Allende and others	Santiago, Chile
July 1990	Neurofibromatosis gene identified	Francis Collins and others: Ray White and others	University of Michigan and collaborating centers; University of Utah and collaborating centers
July 1990	*Science* Commentary opposing genome project	Bernard Davis and colleagues	Harvard Medical School
July 1990	OTA Report on DNA forensics	Robyn Nishimi and OTA staff	Office of Technology Assessment, US Congress
July 1990	Hearing before Committee on Energy and Natural Resources	Senators Wendell Ford and Pete Domenici	US Senate
July 1990	International conference on ethical and legal implications of genome mapping and other advances in genetics	Council of International Organizations of Medical Sciences	Tokyo and Inuyama City, Japan
September 1990	First NIH genome center grants	Jane Peterson, Linda Engel and staff of the National Center for Human Genome Research	National Center for Human Genome Research
September-October 1990	Second DNA Sequencing Conference	J. Craig Venter and Walter Gilbert, organizers	Hilton Head Island, South Carolina
October 1990	**Genome project «officially» begins**		
November 1990	Second international workshop, on ethical issues in genome research	Santiago Grisolía and colleagues	Valencia, Spain

BIOETHICS IN THE EUROPEAN COMMUNITY

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Introduction

The purpose of this presentation is to tell you, in a very factual way, what is going on in the European Community (EC, European Union since 1992) as far as bioethics is concerned:

My remarks will cover three areas:

1. The first is that, to paraphrase the French revolutionary Saint-Just on happiness, *bioethics is a new idea in Europe.* I mean that the EC has become aware of the importance of this topic only very progressively.

2. Second, this progressive awareness *has led to the creation of new bodies,* the future of which in my opinion is promising.

3. Third, I will try to roughly define *the principles of bioethics* which have already been formulated by the EC.

A progressive awareness

1. Why

One can easily understand why the EC took some time before focusing on problems of bioethics:

a) First of all, one must consider that in 1957, when the Treaty of Rome was signed, the word bioethics did not yet exist (biomedical ethics).

b) But, chiefly, as you well know, the aim of the EC was until recently to create an economic market, not a political or cultural union.

2. *How?*

Nevertheless, little by little the EC became aware of the importance of discussing the social consequences of new technological applications, as well as of the importance of better comprehending public reaction toward progress.

The advent of the «green» movement and the environmental movement prompted the EC to also develop an ethical dimension to environmental protection. Thus Eurobarometer, launched by the Commission as a vast programme of public surveys in each European country, began to address issues of bioethics. Public opinion polls were carried out as part of this programme in order to inform the Commission on how people perceive the rapid technological and scientific advances affecting their lives.

But the watershed was the moment the EC decided to finance its own research programme on the human genome in 1989.

There were great debates in the Parliament. It was finally accepted that a set percentage of this programme's budgeted funds would be earmarked for study of the social, legal and ethical implications of the Human Genome Project.

Even more surprising was the legal text of the Council of Ministers Decision launching this research programme. Indeed, the Ministers decided to immediately express their strong views as to how the potential research findings should be used and not abused. By way of example, they clearly prohibited any form of germ-cell therapy.

Since then bioethics has acquired a greater and greater presence in European debates. As has already been underscored, it was at the heart of the debates over four Directives, drafted in 1988, on biotechnology.

a) The aim of the first of these directives was to protect persons working at genetic laboratories from the risks of occupational disease. This Directive did not take effect until November 29th 1993, and its transposition into internal law is still pending.

b) Two other directives were drawn up in order to prevent the risks involved in the confinement or dissemination of genetically modified organisms.

These three directives, now enacted, display an effort to reconcile academic freedom with the need to protect human health and the environment.

The two Directives (90/219 and 90/220) refer, respectively, to confined use of genetically modified organisms (GMO) and to the intentional release of such organisms. Both took effect on October 23rd 1991 and most Member States have transposed them to their national laws. Nevertheless, an action for non-transposition on the grounds of lack of competence by the Commission has been brought before the Court of Justice of the European Communities. Indeed, the Commission considered indispensable a strict enforcement of safety-rule compliance by genetic engineering laboratories. Its enactment in German national law apparently entails certain difficulties for the German government and research. The provisions adopted at the national level are in fact very rigorous.

These difficulties raise the need for evaluating within a specified time period the conditions for applying said Directives in the different Member States, given the importance of the scientific, economic and ethical aspects.

c) The last directive refers to patenting life, which has not yet been adopted. It bears highlighting that this is so because of ethical objections raised by the Parliament.

Originally, the draft Directive did not even mention any ethical problems raised by the patenting of living material. But the European Parliament proposed several amendments to the draft Directive, voicing some of the main concerns arising from ethical consideration.

The European Commission advisory group on biotechnology ethics (see further below), on their own initiative, issued a report on this Directive proposal, in view of the following critical ethical problems:

– The inherent propriety of patenting living beings;

– patents and respect for the principle of the non-commercialization of the human body;

– use and patentability of transgenic animals;

– the Directive's compatibility with the «biodiversity» principle proclaimed by the UN Treaty signed in Rio de Janeiro in late 1992 (and ratified by the European Union) [1].

The advisory group had particular regard to the concerns expressed in the Parliament with respect to:

– Parliamentary fears that patenting life could lead to endorsing the possibility of commercializing parts of the human body.

– Similar fears of possible legalization of patents on transgenic animals, which was opposed by a recent resolution passed by the Parliament.

– Parliament is in fact dealing more and more with problems of bioethics, even where they outstrip the sphere of competence of the EC. Some examples which I can give you (which have to do more with biomedical ethics than with the human genome) are:

– The resolution of IVF (Gossini).

– The Parliament's discussion of euthanasia (Schwartzenberg).

Draft report on prenatal diagnosis (Pompidou)
This report grew out of the 1991 Commission communication on the competitiveness of Community bioindustries, in relation to the imperatives protecting the environment and safeguarding individual and collective rights (Mrs Breyer).

The Parliament also held an in-depth discussion on the Community's fourth research programme, which includes specific research programmes in ethical aspects:

– Biomedicine and Health (bioethics research is therefore also included within this programme).

– Biotechnology (the goal is to enhance basic biological knowledge, permitting applications in the agricultural, industrial, healthcare, food and environmental fields).

– Environment (including research on economic and social, and hence ethical, aspects, of ecological problems).

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[1] As a consequence of the above-mentioned advisory group report, the Council of Ministers adopted, on the proposal of the Commission, a common position on February 7th 1994, and the definitive adoption of the Directive is foreseen for late 1994.

– Life technologies for developing countries (the idea is to explore in relation to these countries improvements in living standards and the health of the population).

Finally, mention should be made of the STOA programme *(Scientific and Technological Options Assessment),* which in September 1992 gave rise to an expert report issued by the Parliament entitled «Bioethics in Europe». This document introduces comparisons affecting seven Member States (Denmark, France, Germany, Greece, Italy, Spain and United Kingdom).

The creation of new bodies

1. Why?

The reasons for creating new Community bodies were quite clear.

Discussion of bioethical issues contributed to bringing about a realization that there existed a cultural gap between a Parliament more and more concerned with the daily problems of citizens and an overly technocratic Commission focused only on industrial interests. Yet as you know, only the Commission has the power to propose new regulations to Parliament and to the Council of Ministers. Thus, aware of the need to bridge this gap, the Commission decided to create new bodies or working groups specializing in the study of legal and ethical issues of biotechnology.

The second reason was Commission concern over some of the public criticism of its regulations. I am mainly referring to the Directive on the use of human blood to make pharmaceutical products (such as growth factor). The EC was accused (unjustly in my opinion) of having likened human blood by-products to pharmaceutical drugs.

The idea, put forward by Commission President Jacques Delors, centres on the believe that scientific progress, as a social phenomenon, cannot be conceived of without citizen support. What is therefore required is better information: serene, clear and honest information. At the Conference «Human Rights and the European Community: toward 1992» held in Strasbourg in November 1989, Jacques Delors drew particular attention to the responsibility of society as a whole and of Europe's duty to be one of the leading voices in the debate over scientific advances: «I would like to see [...] the debate continue on philosophical and ethical grounds such that as science progresses so, too, does our conscience».

2. *How?*

In order to respond to the questions raised by a public which did not understand how parts of the human body could be regarded as mere commodities, the Commission and Council decided to create, in addition to the informational campaign launched by the Parliament, different working groups:

a) The *HER Group (Human Embryos and Research)* brings together outside experts and has issued two reports on the pre-embryo (1992) and the post-implantation embryo (1994).

b) The *ESLA Group (Ethical, Social and Legal Aspects of Human Genome Analysis)* is funded by means of a 7% reserve at the Human Genome Programme promoted in June 1990 by the Council in order to study the legal implications of said programme. It has issued one report (December 1991), which will be completed in late 1994.

c) The Commission, moreover, has adjusted its internal structure in order toenhance its involvement in the ethical debate. Thus, in 1992 a *Bioethics Unit* was created, within the Directorate General on Research (DGXII), to fund research in this field pursuant to requests made by Member States.

d) The Commission's Secretariat General likewise established in 1994 a *WorkingGroup* to assure consistent Commission positions on bioethical matters vis-à-vis non-EU parties (the group is specifically working on the preparation of the Framework Convention on Bioethics of the Council of Europe).

Lastly, and above all, the Commission set up a permanent advisory group, of which I am a member. Our role is to help the Commission to clearly identify the ethical problems raised by the development of biology, genetics and biotechnology.

The statute of the biotechnology ethics advisory group is original. Its creation was guided by three main ideas:

1. The biotechnology sector is key to the economic development of the Community (9% of the labour force and of the gross value added in the European Union).

2. This technology will thoroughly change the approach to health care (predictive testing, gene therapy), revolutionize farming and livestock breeding, and renovate methods for combatting pollution. It potential economic impact is immense.

3. Europe, however, demands that the changes taking place be given serious thought from a not purely utilitarian viewpoint. More than ever the construction of Europe demands permanent social dialogue based on ethical and humanist values.

This was the message delivered by President Delors at a Brussels press conference to announce the group's renovation, after its president, Marcelino Oreja, European Parliament member for Spain, was appointed European Commissioner for Transportation. Thus, as president of the group, I have the honour of following in Mr Oreja's footsteps.

I must point out that the group is not an integral part of the European institutions; it is completely independent and charged with submitting non-binding advisory opinions to the Commission to guide the latter's thinking and actions.

These opinions may be issued at the request of the Commission or on its own initiative on affairs deemed critical.

Its work turns on three main axes:

1. Identifying and defining ethical problems tied to with advances in the life sciences and their technological applications.

2. Evaluating the ethical aspects of Commission activities in the biotechnology field-be they the drafting or application of Directives, selection of research initiatives or support for industrial development.

3. Advising the Commission as to the information to be taken into account and reported to public opinion.

The *group has been enlarged,* going from its original six members to nine in February 1994. These experts do not represent countries or institutions. They form a completely pluridisciplinary team and are to take into account all facets of European culture. The group chairperson is elected from among its members [2]. The

[2] In addition to myself the members are: Anne McLaren (United Kingdom), Foreign Secretary of the Royal Society, member of the Nuffield Bioethics Committee, member of the Human Fertilization and Embryology Authority; Margareta Mikkelsen (Denmark), ex-head of the Department of Medical Genetics at the John F. Kennedy Institute, member of the Danish Council of Ethics; Luis Archer (Portugal), Professor of Molecular Genetics at the Biotechnology Department (Lisbon), member of the Portuguese National Council of Ethics; Gilbert Hottois (Belgium), Professor of Philosophy, Co-Director of the Centre for Interdisciplinary Investigations in Bioethics of the Free University of Brussels, Co-Director of the CRIB at the same university; Dietmar Mieth (Germany), Professor of Ethics and Theology, President of the Centre of Ethics of the Natural Sciences and Human Sciences at the University of

group secretariat is located at the Secretariat General of the Commission.

The *group's work* takes up ethics in the broadest sense. Our basic evaluative criteria are essentially:

– respect for humanist values and human rights,
– consumer protection,
– freedom of investigation,
– economic and social progress,
– inter-Community solidarity with the less wealthy countries,
– biodiversity linked to sustainable development.

During its first mandate, the group addressed pressing issues on its own initiative (review of the directive proposal on patents) and at the request of the Commission (BST - transformation of human blood derivatives).

The three opinion reports issued until now are summarized below:

a) In connection with the genetically engineered *bovine growth hormone* called BST (bovine somatotropin) which is administered to cows in order to increase their milk production, the group concluded that use of this product would not involve ethical problems provided that consumer health was rigorously safeguarded. It stressed the potential problem of presence in the milk of antibiotics administered to cows suffering from mammitis brought on by BST use. It insisted on the need for consumers to be informed as to the origin of the products offered them (labelling).

b) In relation to *human plasma and blood by-products,* the group has concludedthat blood derivatives should be treated as rigorously as medicines; donations should continue to be anonymous, voluntary and free, and the public authorities should exercise control in this area.

c) With respect to *intellectual property in biotechnology* the group's thinking was in line with the principles derived from the Human Rights Convention. It asserted the need for an international agreement to resolve the problems of the hu-

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Tubinga; Octavi Quintana Trías (Spain), Advisor to the Director General for Public Health, President of the Bioethics Steering Committee of the Council of Europe; Stefano Rodotà (Italy), Professor of Civil Law, member of the Ethics Committee of the National Council of Research, Deputy in the Italian Parliament; Egbert Schroten (Netherlands), Professor of Christian Ethics at the University of Utrecht, Director of the University Centre for Bioethics and Health Legislation.

man genome's patentability, the subject of heated discussion as a result of the patent application filed by the United States NIH (National Institutes of Health Craig Venter's Laboratory). This report was issued in a context that highlighted the political nature of the group's activities. As the study of this subject coincided with the debates in the European Parliament, the group rapporteur was able to exchange information with the Parliament speaker as well as with experts at the Council of Ministers. Thanks to these contacts, the document served as a catalyst for the stands taken by the Commission and the Council, and strengthened the decision-making process.

In addition to the subjects on which it has already issued opinion reports, in 1994 the new group has studied three other areas:

Prenatal diagnosis
The group spontaneously took up this issue due to its direct link to a very serious ethical matter: the voluntary interruption of pregnancy. The fact is that while research advances in microbiology and genetics increasingly permit congenital defects to be detected in the fetus, medical knowhow as to how those anomalies can be corrected prenatally is still quite limited. Hence, the question of voluntary abortion arises with greater frequency. Among the specific aspects which will be taken into account are the rights and responsibilities of the parents and physicians, confidentiality of medical records, and the dignity of all human beings, handicapped or not. The works of the Council of Europe and the European Parliament (Pompidou report) will be considered.

Gene therapy
The group began this inquiry at the request of the Commission. While somatic gene therapy, that is, genome corrections which only affect the patient, does not appear to pose specific ethical problems, it will nevertheless be necessary to reconsider questions of risk-benefit, respect for the patient's dignity, informed consent, etc. I should point out that this new treatment will be the subject of a centralized proceeding of the European Pharmaceutical Agency. Conversely, in germ-line gene therapy the new or modified traits are passed on to the patient's offspring, raising entirely new ethical questions which the Commission must begin to examine.

Animal transgenesis
The Commission has similarly asked the group for an opinion on the ethical aspects of activities involving animal transgenesis, that is, the genetically engineered creation of animals possessing some utility for human beings. Mindful of the wellbeing of the animals modified by such procedures, the group concentrates its study

on human health, environmental protection, biodiversity and aspects relating to the creation and evolution of species.

The bioethics principles already formulated

Before examining these principles I want to emphasize that the EC has put into practice a new approach to economic issues that gives a prominent place to ethical considerations.

1. The Fourth Criterion

The EC is attempting to define what is called the *Fourth Criterion.* When drafting any regulations concerning the marketing of new products or services, this new criterion, in addition to the classic quality, safety and effectiveness benchmarks, says that the social acceptance (pharmaceutical drugs) or rejection (medical intervention) of the product or service must be taken into account.

The Commission is now convinced that the EC cannot throw its support behind advances unless they are accepted, or at the very least understood, by the public at large.

2. The defence of human rights

Also noteworthy is the EC's defence of human rights when dealing with issues of bioethics. I must stress that all the main principles of bioethics have already been accepted by the EC; for example:

- academic freedom and the necessity of sharing scientific knowledge;

- the protection of the human species and human diversity (as I already mentioned, the EC has signed the UN Treaty on Biodiversity drafted in Rio in 1992);

- the respect for the dignity of the individual, in an age when the human body can be used for medical or industrial purposes;

- the need to prevent any breach of the confidentiality of medical data (a Directive has been drawn up on the protection of personal data).

Recall that article F of the Treaty on European Union for the first time refers to the European Convention on Human Rights and the constitutional traditions of Member States as sources of Community Law.

Conclusion

As you can see, bioethics has come to occupy a major role in European policy. And it is readily foreseeable that this role will be enlarged for a number of reasons:

1. First of all, as a result of the ratification of the Maastricht Treaty:

   a) The Maastricht Treaty attributes new powers to the EC in matters of health care and the design of social policy. The EC will have to regulate the use of genetic elements, particularly with regard to workers, in accordance with the principle of non-discrimination.

   b) The Treaty also gives new powers to the Parliament, which will thus be able to exert a stronger influence on the Commission and Council of Ministers as the decision-making bodies. And as you know the Parliament is greatly concerned with ethical problems.

   c) The Treaty's goal is to create a political union, which means that public opinion will also be more influential and that the EC will have to take into account public uneasiness over rapid advances. In this period, bioethics should afford European institutions an opportunity to be more responsive to public opinion.

2. The second reason stems from the existence of a system of legal integration. I mean that the European Court of Justice directly applies European law to the citizens and does so in accordance with the «common legal traditions» of the Member States, which has just been set down in the Maastricht Treaty.

This is why I believe that, notwithstanding that each State has different legislation, the basic principles of bioethics will be commonly applied throughout the EC as a common cultural background. And this is of considerable importance for constructing Europe, when we consider that by the end of the century more than 80% of general regulations will be inspired by European law.

THE STATE OF THE ART

PRESENTATIONS

INTRODUCTION

Carleton Gajdusek *

1976 Nobel Laureate in Medicine, Head of the Laboratory of Central Nervous System Studies, Bethesda, Maryland. United States of America.

Now we are going to hear about the genome alone determining genetic variability; but the genome alone does not determine human variability. The hard wiring of the brain is very largely determined by environmental software of sensory input. Simply a patch on the eye of a cat completely restructures the cat's processing of visual information. The patch that the experimenter puts on the cat's eye does not appear in the map of the genome; the brain is differently restructured as a result. A restraining band on an extremity restructures the processing of information in the brain of the developing human or animal. The person who binds the hand or patches the eye is not to be found in the genome. In a more subtle way, our culture and the grammar and the phonemes of our language structure the brain. Whether we write phonetically or idiographically produces differences in processing nerve nets which are not to found in the genome. There is no need to believe that all our human individuality and individual variability is violated by scientific intrusion into our genetic basis.

On the other hand, we only have to look at different personalities and learning capabilities of different breeds of dogs, to know that

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* Moderator.

genetics play a determining role. Learning of spoken language and of writing give proof of environmental effects on the structure of the human brain, as has the study of amblyopia ex anopsia and eye-patching in infancy. Extreme forms of heredofamilial embryonic brain malformation such as severe anencephaly and microcepahly are lethal, but others are non-lethal and produce problems in our human community. Superimposed on the genetic brain endowment we have the effects of environmental programming. There is no way from the map of the genome to see potential ability. Plato's Socrates, Mozart's father, or Alexander's Phillip do not appear, yet they determined brain structure and function, to a large part, and thus the potentiality of their protégés' genetic endowments.

We are now going to turn to what we expect to find by mapping the genome. I thought that a cautionary note that all there is in the brain is not to be found in the map of the human genome should always dominate our thinking and our potential fears. We shall turn to the discussion of where we really are in the mapping; i.e. determining the nucleotide sequences for the genes that determine our cellular responses to the environment. This mapping is already proceeding rapidly in hundreds of laboratories. My own laboratory has located several dozen mutations causing fatal CNS disease in the period of a couple of years. These may seal the fate of those individuals who carry them, in that they will develop dimentia or severe, quickly fatal CNS diseases at an early age. We often know this already for many members of their family, and we often know which members of their family do or do not carry these mutations. We are meeting to discues what to do with such information. To whom does it belong? Who wants to exploit it and make cash out of it? Who wants to put restrictions on the individuals who are known to be carriers of these deleterious genes? These are the problems of this meeting.

SOME THEORETICAL COMMENTS ON GENETIC POLYMORPHISM AND INDIVIDUAL VARIATION

Hamilton O. Smith *

1978 Nobel Laureate in Medicine, Professor at the Johns Hopkins University School of Medicine, Maryland. United States of America

There are an estimated 100,000 genes in the human genome, and with few exceptions, every individual has the same basic set of genes. However, omitting identical twins, no two individuals are alike. How then do individual differences arise? They arise because genes frequently occur in several versions (alleles). If as few as 1% of our genes occurred in two equally probable versions, then $2^{1,000}$ combinations would be possible. Actual estimates are that about two-thirds of all genes are polymorphic, and that any given individual is heterozygous for about a third of his genes. Thus an almost limitless variety of individuals is possible.

An extreme example of polymorphism is in the HLA complex of genes which determines tissue transplant rejection and foreign antigen response. The HLA-A gene, which is only one of several genes in this cluster, has up to 50 alleles. Cloning and sequencing of this gene from different individuals has revealed extensive variation, with some alleles differing in as much as 10-15% of the amino acid residues of the HLA-A protein. Another well studied example of polymorphism is in hemoglobin. In some populations,

* Moderator.

the beta chain gene of hemoglobin is present at about 90% in the normal A form and 10% in the S (sickle) form. The S allele differs from the A allele by only a single base substitution resulting in a single amino acid change in the hemoglobin beta chain, but this makes a significant difference in the physical properties of the hemoglobin protein. Heterozygous AS individuals have greater resistance to malaria than AA individuals, Selection for heterozygosity results in a balanced polymorphism among individuals living in regions with a high incidence of malaria. Numerous examples of polymorphism are recorded in the Genome Data Base (GDB), many of which are associated with inherited disease.

The extensive individual variations seen for almost all human traits (physical appearance, intelligence, musical ability, and so forth) can be explained in terms of genetic polymorphism. Polymorphisms can theoretically be of two types: (1) variation of the coding sequences, and (2) variation of flanking non-coding regulatory sequences. Human genes generally consist of several exons (sequences that code for amino acids) separated by intervening introns (non-coding sequences that are removed by RNA splicing). Often several hundred basepairs of sequence upstream (5') to a gene are involved in expression of the gene. Sequences in this region contain the promoter and a number of DNA sites at which regulatory proteins (transcription factors) interact to control the rate of transcription. The introns contain information for correct splicing. Incorrect splicing can yield inactive protein or protein with altered function. Downstream (3') sequences direct termination of transcription and polyadenylation of the 3' end of the messenger RNA. Polymorphic variation in non-coding DNA could thus influence the amount, tissue specificity, and temporal order of gene expression. This could be a major factor in the determination of human traits. It has been argued by some that we will have most of the important information contained in our genome by sequencing just the coding parts as represented in messenger RNA. One could argue, however, that at least an equal amount of information resides in the DNA regulatory regions of each gene. In fact, a gene should perhaps best be considered as a unit consisting of all coding and controlling sequences.

A major goal of the Human Genome Project is the mapping and sequencing of all the human genes. One must add to that the task of cataloging the sequences of all allelic variants in the human population, particularly those associated with clinical disease. Identification and detection of genetic variants that predispose to disease, although already well underway, will become an even greater factor in the medicine of the next century.

Detection of genetic variants can now be done at the DNA level using two powerful, recently developed methods: the polymerase

chain reaction (PCR) and the ligase chain reaction (LCR). PCR utilizes two oligonucleotide primers, one for each strand of the chromosomal DNA template. These are directed convergently, so that a cycle of replication copies the region of the DNA between the two primers. At every cycle, the DNA product of the reaction can serve as template in the next round of primed replication, hence an exponential chain reaction is initiated, with an approximate doubling of product at each cycle. The sensitivity is such that the DNA of a single cell can be analyzed. Genetic variants are detected in several ways. If deletions or additions of sequence are present in the DNA, the PCR product will be either smaller or larger than expected. Base substitutions can be detected by first amplifying the region containing the base change, and then probing with an oligonucleotide complementary to a small region of sequence overlapping the base change. A single base mismatch can strongly affect the ability of the oligo probe to hybridize to the sequence. Single base detection can be multiplexed by attaching multiple oligo probes, each specific for a different base change, to a membrane filter strip as a matrix of dots. The labeled PCR product can then be hybridized to the filter strip and after suitable development, the pattern of positive and negative dots determines the genotype.

LCR, while not yet routinely used, has possible advantages for single base detection. Four oligos are required, two flanking the base in question on each strand, so that ligation only occurs if the mismatch is present at the mutated site between the oligos on either strand. A thermostabile ligase is utilized and rapid cycling is carried out as in PCR. Again, the crucial feature is that the ligated products of each cycle act as templates in subsequent cycles, producing an exponential reaction. LCR reactions can be multiplexed as with PCR.

Application of these techniques makes it possible to generate genetic profiles which identify the particular alleles carried by any given individual. When targeted to alleles associated with disease, such profiles allow presymptomatic detection. In the next century one could also imagine the application of these methods to the prediction of human traits at an early age or even in-utero. Important ethical issues are raised by such possibilities and will ultimately have to be resolved.

GENES AND HUMAN FREEDOM. WHAT IS DISTINCTIVE ABOUT GENETIC DETERMINANTS OF A PERSON FATE'S?

Daniel Wikler *

Professor of Medical Ethics at the University of Wisconsin. United States of America.

Ordinary medical conditions –a weak heart, for example, or a brain tumor– limit one's freedom to do as one pleases. So do genes. Why should genetic information be thought to pose a *distinctive* question about human freedom?

Perhaps the most logical answer is that it should not. Genes partially determine one's fate, but so do monogenetic conditions of one's body. Genetic information is not necessarily a more powerful predictor, nor are those whose forecast are less vulnerable to avoidance by self protective actions of the individual. To be sure, genetic predispositions to a particular morbid state may be impossible to counteract, but so too may the delayed effects of trauma or infectious disease. These considerations suggest that advances in genetic science pose no new or distinctive question about human freedom, at least when considered in general and in the abstract. Genes are physical attributes like any other, knowledge of which may be used for good or ill.

False beliefs and spurious associations, however, can be particularly influential in the field of genetics, as the victims of the old

* Rapporteur.

Eugenics know well. Thus it is useful to sped late on the reasons that genetic information might be *thought* (however irrationally).

Identity

We define ourselves largely in terms of our kin: our family, our ancestors, our people. Genes link us with their behavior, customs, and destiny: «Apples do not fall far from the tree». Genes thus represent a way in which our freedom is limited by the *past.*

Essence

The metaphysical doctrine of «essence» and «accident» distinguishes between attributes one may add or shed and attributes the loss of which would amount to one's extinction. Consider the futility of wishing that you had been born to different (and better) parents. That person might be happier than you are, but he or she would not be *you.* It makes perfectly good sense, however, to wish that you were not diabetic, or lame. That person might be happier, and *would* be you. Our genes are understood as essential to who we are. Genes thus determine who we are in the *present.*

Fate

Fatalism is a superstitious belief which is sometimes confused with the more plausible notion of determinism. Determinism is simply a recognition of the universality of cause and effect, the governance of the laws of nature. Fatalism mantains that certain events, e.g. one's own death, will occur at a preordained time regardless of intervening causes and effects.

Perhaps because of linkage of genes to both identity and essence, genes may be more likely than ordinary medical conditions to seem to impose a fate on a person regardless of how he conducts himself. Genes are thus a link to one's *future,* and it is understandable that genetic information may be especially *feared* –and also that it might contribute more than it should to harsh and discriminatory treatment at the hands of others.

None of these considerations should sway educated and rational people. For example, most people inherit their family's culture along with genes, and the relative influence of the two is notoriously easy to confuse. The believe that genes are a *direct* and distinctive limitation on one's freedom is understandable, and powerful, and potentially dangerous. The notion that genes represent our future, our present, and our past –whether presented as a scientific theory or as a folk belief– is a fitting subject for public education in bioethics.

THE HUMAN GENOME PROJECT: STATE OF THE ART

Ann Victoria Thomas *

Attorney, Office of the General Counsel, University of Kansas. United States of America.

From a medical standpoint, it is important to know why we as humans are different if we all have the same genes. We are different because there are minor variations in the genes. The sequencing of the genes and the discovery of the variations is important. This would allow us to predict disease traits as well as human traits.

The genome alone does not determine human variations. Brain function and environment influence variations.

To understand the amazing variation of the genes will require us to improve our present analytical methods by a factor of 1,000. We have all this diversity because of evolution. It is better to have great diversity in order for the species to survive.

At this time, about 20,000 of the estimated 100,000 genes have been sequenced. We expect that all 100,000 will be known within the next 2 years. On the other hand, we estimate that there are 12 to 15 million differences between individuals. Eventually, we should be able to determine which genes change with evolutionary events.

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* Rapporteur.

The greatest progress in the Human Genome Project has been made without technological advances. Much of the progress has come from the use of robots. The electrophoretic run time is the limiting factor. Through the use ot new techniques, it is likely that we will improve by two orders of magnitude sequencing time within 2 years.

It is important in the genome project to consider its relation to the study of congenital defects. The basic strategy for prenatal genetic advice involves the need to detect the risk factors. The discovery of this kind of information will give rise to ethical and legal issues which wiil cause us to develop legal codes to deal with the issues.

Comments of the moderators

Harrison O. Smith: From a medical standpoint, it is important to know why we as humans are different if we all have the same genes. We are different because there are minor variations in the genes. This is known as genetic polymorphism. Two-thirds of all our genes are polymorphic at a significant level. This results in an uncountable number of possible combinations. The sequencing of the genes and the discovery of the variations is important. The technology for detecting variations is rapidly advancing. This would allow us to predict disease traits as well as human traits.

Carleton Gajdusek: The genome alone does not determine human variations. Brain function and environment influence variations. For example, putting a patch on the eye of a cat changes the way the cat processes information. This is not in the gene. Language and culture structures the brain. Dogs have been manipulated through breeding by humans to change their personalities. As another example, you cannot detect Mozart's father in the gene. In considering what we expect to find from mapping the genome, remember that the genome does not determine everything.

Comments of the participants in the round table

Charles Cantor: While maps of the chromosomes show that we are all very similar, the microscopic detail shows amazing variety. To understand this variation will require us to improve our present analytical methods by a factor of 1,000. How will we do this The model is found in computer science. Current computers do things fast and they do more than one thing at a time. This is called parallel processing. Sequencing by hybridization is another improvement in technique.

For present DNA sequencing methods, 20,000 base pairs can be produced per worker per day. The best labs can produce at a rate 10 times faster than this, but 10^8 base pairs per day per scienist should be possible. Keep in mind that DNA analysis (genetic testing) is not the total answer. For example, there are discordant identical twins, i.e. mirror twins. They have identical genes but *they mirror each other.* It would take 6×10^{16} to characterize all gene differences. Why do we have all this diversity? This is because of evolution. It is better to have great diversity in order for the species to survive. Evolution does not care about the individual, only the species.

Craig Venter: It is difficult to distinguish human proteins from animal proteins. The genes are different, but the proteins are identical. At this time, about 20,000 of the estimated 100,000 genes have been sequenced. In 1990 only 2,000 had been sequenced. We expect that all 100,000 will be known within the next 2 years. On the other hand, we estimate there are 12 to 15 million differences between individuals. Every cell in the body has the same chromosomes, but each cell processes differently. For example, heart cells express differently than liver cells. Heart cells from humans down through insects are more similar than heart and liver cells. The Institute for Genomic Research uses parallel computers in its research and already 200 computers have been saturated. Eventually, we should be able to determine which genes change with evolutionary events. The Institute for Genomic Research also studies research policy and ethics. Keep in mind that human beings will use whatever information they can for discrimination.

Victor Walter Weedn: The development of technology is a big part of the Human Genome Project. Major sequencing technological breakthroughs have not yet occurred. The first commercial automated sequencers were not developed for the genome project. The greatest progress in the Human Genome Project has been made without technological advances. Much of the progress has come from the use of robots. The electrophoretic run time is the limiting factor. The greater the voltage applied across the gel, the faster the run time. But the more voltage applied, the more heat. Keep in mind that «more is less». Ultrathin gel allows for faster analysis. Capillary gels are even more efficient and also much less expensive. The microchip can revolutionize molecular biology. Mass spectrometry may also be a solution. It is likely that two orders of magnitude greater sequencing time will occur within 2 years.

Bartolomé Jaume Roig: In 1534 a physician first created an anatomical map of humans. Now we have moved to a microvision of the map. It is important in the genome project to consider its

relation to the study of congenital defects. Behween 5 and 7% of newborns have these. They can be chromosomal, heriditary, or congenital malformations. As to chromosomal defects, 100% of these can be diagnosed prenatal. As to heriditary disease, 1.4 to 2% of all newborns have these. Only 60% of these can be determined prenatal, such as cystic fibrosis and Huntington's disease. As to congenital malformations, the incidence is three to four percent and 80 to 90% can be diagnosed prenatal. The important of these three conditions is that they result in 20% of the deaths of children under 1 year of age and 85% of the first quarter spontaneous abortions.

There are various levels of prevention. This can be pre or post natal. As to post natal, the best prevention would be based on having as much information as possible about the individual. Post natal investigation can detect carriers. All this information has to be clear, concise, and objective when it is presented to the couple. We must then respect the decision of the couple. For those diseases which are detected neonatally, treatments must be efficient.

There are geographic areas which have more incidence of certain diseases. For example, neural tube defects appear more often in the United Kingdom. Carrier frequency is also important to view, for exaple in Tay Sachs disease.

The basic strategy for prenatal genetic advice involves the need to detect the risk factors. This involves family background, age, ethnic background. There are two techniques of prenatal diagnosis, non-invasive such as ultrasonography and X-rays, and invasive such as biopsy of the fetus or amniocentesis. The discovery of this kind of information will give rise to ethical and legal issues which will cause us to develop legal codes to deal with the issues.

Andreas Klepsch: In the mid '80's the time was right to make a coordinataed effort to sequence genes. The genome as a whole is the focus. It would take a pile of paper 72 meters high to describe the human genome. The European Communities human genome project started in earnest in the late '80's. It had several major tasks. These included improving the genome map, improving the data bases, improving the applications in medicine, and improving the physical map. One of the conditions of the project was free access to the resources for all European scientists, and sharing of information. There are legal, economic and social issues growing out of the project. Thus, a project was set up to consider the legal, economic and social aspects. This will result in the publication of a number of studies on these issues. There are areas of biomedical research such as analysis of the human genome, research on biomedical ethics, improvement of

the physical map, data handling, DNA sequencing, and improvement of the genetic map. Currently, we are discussing what to do in the next program. A question to be answered is whether going directly to sequencing now or in 2 years makes sense. We have no good idea of what 90% of human DNA is for. This has an impact on future human genome projects. We need more work on identifying the functions of DNA.

Discussion

In the discussion following the round table, some of the following points were made.

- *There are genetic conditons which only «penetrate» in certain environments, i.e. they may not have any effect in one environment but may be lethal in another.*

- *Keep in mind that processing of information by the brain is primarily environmentally determined.*

- *We know only very little about the proteins. To learn about proteins, we have to study the genes.*

- *Many genetically engineered plants have been wiped out by pathogenic microbes which can evolve faster. This has great implications for altering human genomes.*

- *The fears about genomic research are the same as they used to be. But the more we discover, the more mysteries there are which will crop up.*

- *Since the Valencia conference, there has been a tremendous increase in the progress of the pronect.*

- *There is a huge difference between genetic therapy for a single individual and attempting to touch the genomic structure of a species.*

PAPERS

THE PROSPECTS OF LARGE SCALE DNA DIAGNOSTICS

Charles R. Cantor

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(In collaboration with Dietmar Grothues, Natasha Bronde, Takeshi Sano and Cassandra L. Smith)

Perspective

The Human Genome Project was initially conceived as a 15 year effort to map and sequence one representative human genome. Because humans are generally rather poor candidates for experimental genetics, it was also agreed to map, and in so far as resources permitted, determine the sequences of a set of model organisms where genetic experimentation is far easier. The real purpose behind all this information gathering is to find the estimated 100,000 human genes and make them accessible to all interested biologists for experimental study. Here the advantage of including the model organisms is that gene knock-out experiments, a powerful test of the putative function of a newly-discovered gene, are vastly simpler than they would be in the human, where ethical and practical concerns would allow such data to be obtained only by retrospective analysis.

To accomplish the initially-stated goals of the Human Genome Project, it was envisioned that at least an order of magnitude improvement in the technology of genome mapping and DNA sequencing would be needed. In fact, initial progress in technology development for human genome analysis has proceeded more

rapidly than anticipated by this plan. In a project less than 3 years old, the state of the art of genetic mapping, physical mapping, and DNA sequencing has already been improved, in each case, by close to an order of magnitude. Most of this has occurred by optimization of pre-existing experimental paradigms. Thus, for example, genetic mapping is rendered far easier by systematic approaches to isolate and characterize highly informative genetic markers like simple sequence repeats. Physical mapping is greatly aided by the availablility of larger insert cloning vectors, and by a variety of applications of the polymerase chain reaction (PCR) to reduce the complexity of DNA samples by selective amplification of particular genome fractions or constituents. DNA sequencing has been accelerated and improved considerably by the use of thin gels, internal fluorescent labeling procedures, better sequence calling software and automated methods for sample preparation.

With the tools available now, the genome project could be successfully completed as originally designed. Indeed, the finding of genes through cDNAs offers the possibility of discovery of most human genes far before the bulk of the genome is sequenced. One way to view these considerable strides in strategy and techniques, is that we should use them to seize as many genes as possible and begin to study their biology. While this is very attractive from many points of view, it fails to take into account that to really understand the function of most human genes, we will need to be able to analyze them in the context of observed human variability. In an ideal scenario, we would like to be able to determine the DNA sequence not just of one human, but of every member of our species. This would allow us to take fullest advantage of the wealth of medical and descriptive data available in order to understand some of the very complex multigenic events which determine key human characteristcs. Such an endeavor is not possible with anything resembling current procedures for DNA analysis.

Future technology

A number of research groups have been exploring new and different schemes for DNA mapping and sequencing, or methods for vast acceleration of existing schemes. These include new cloning methods, new methods for mapping larger numbers of clones, and totally new methods for DNA sequencing. Given the wealth of ideas and the considerable investment that is being made, it seems quite likely that, a decade from now, methods for DNA manipulation and sequencing will be orders of magnitude faster than they are today. In this presentation, we will stress some of the methods that our laboratories are currently engaged

in. However, much as we are attracted to these particular implementations, there is no guarantee that our particular approaches will be the ones that ultimately prove most useful. But, a description of the methods and their potential advantages will reveal some of the basic, general considerations that must enter the creation and optimization of new strategies for DNA analysis.

The magnitude of the task involved in large scale diagnostic DNA sequencing is staggering by current standards. An estimate for the variability of any two human chromosomes is 0.2%. Thus within any single genome there will be 6 million DNA differences due to heterozygosity. As many as 12 million DNA differences might be needed to yield of full comparison of any two complete genomes. It is not sufficient in such comparisons to consider just exonic DNA. Many disease alleles fall in intronic regions, and the prevelance of changes in control sequences or introns on the level of gene expression or the utilization of alternate splicing pathways cannot really yet be estimated. For all of these reasons, it would be ideal if methods could be developed that would characterize all differences in a given genome from an arbitrary norm. There is no method yet described that looks only at DNA differences. Supposing that such a method is found, eventually, for diagnostic DNA sequencing to be cost effective, the method would have to allow the set of differences to be found in less than one work day. Thus we need to plan for DNA sequencing techniques that would provide anywhere from 10^7 base pairs per day (if differences can be highlighted) to more than 10^9 base pairs per day, if extensive regions must be fully sequenced. These rates are 10^2 to 10^4 faster than the very best that can be done with current technology. Lest these numbers seem ridiculous, it should be kept in mind that the ordinary bacterium, *Escherichia coli,* determines DNA sequence continuously at the rate of 2×10^8 base pairs per day, as it replicates its DNA. If only we could get it to tell us what it is doing, the task of DNA sequencing would become trivial.

Two general approaches can be conceived to gain tremendous increases in the rate of DNA sequencing. The first is to increase, dramatically, the rate at which a single DNA sequence can be read. Potential approaches for doing this include mass spectrometry, or single molecule detection. The second general approach, and the one we will concentrate on here, is the parallel analysis of many different DNA species. The simplest version for doing this is to build conventional electrophoretic DNA sequencers with large numbers of parallel lanes. Another approach is to sequence many different DNA molecules as a mixture by differential labeling. In such multiplex methods, the labels can be applied simultaneously, as in the use of large numbers of different fluorophores, radioisotopes or stable metal isotopes, or serially,

as in the example of successive filter hybridizations, currently in use by several different groups of investigators.

If very great increases in DNA sequencing speed are achieved, it is important to realize that the distinction between the mapping and sequencing stages in DNA analysis all but disappears. In current DNA analysis, mapping provides ordered samples for sequencing, and the resulting map information helps orient and subdivide the clones used in the actual sequencing project. In the large scale comparative DNA sequencing needed for diagnostics, the prototype sequence norm replaces the need for map information. What remains of the map is the set of DNA samples that will be sequenced. How these samples will be obtained and handled in an orderly fashion for diagnostic DNA analysis is a major unknown. If, for example the sequencing method used is optimal with 10^3 base pair targets, more than a million targets must be selected and distinguished. At present, the only conceivable way to select these targets and purify them from the genome without extensive subcloning is by PCR. Whether more efficient approaches can be designed in the future remains to be seen.

The implications of the need to handle large numbers of DNA samples have led us to focus our attention on mapping and sequencing methods where large arrays of targets or probes are used. In principle, the power of such methods can be extended almost indefinitely by using larger and larger array, in the same way that computer chip technology, thus far, has shown almost no bounds on its expandability. Although today's arrays are usually dots on filters, surely future arrays will be smaller and will begin to resemble the silicon chips used in microelectronics. For this reason it is already customary to refer to such materials as sample chips or oligonucleotide probe chips.

We will give two examples of the approaches we are taking to explore the use of arrays in faster DNA analysis. The first is a mapping project, which was recently completed. Here the goal was to order a five-fold redundant cosmid library covering the genome of the yeast *Schizosaccharomyces pombe*. This 15 Mb genome is roughly a tenth the size of a typical human chromosome, and we felt it was an excellent benchmark against which to test a new strategy. Conventional methods for probing an array of cosmids use relatively simple DNAs as hybridization reagents. Such probes will usually only detect a few cosmids in the array. This is a fine approach if the goal of the experiment is to find a cosmid corresponding to a particular probe of interest. It is an extraordinarily inefficient approach if the goal is to order the library.

We have developed procedures to use very complex DNA samples as probes. Pulsed field gel electrophoresis (PFG) is used to

separate large DNA fragments from the organism of interest. These are radiolabeled and used directly to interrogate a cosmid array. This allows a very rapid assignment of cosmids to bins that correspond to particular fragments. Then, higher resolution PFG separations are used to prepare non-overlapping sets of DNA fragments from the genome of interest. These size fractions represent pools of probes. They are also radiolabeled and used to interrogate the array. Eventually a profile of hybridization of each cosmid to a panel of 60 to 80 different probes is developed. A likelihood method is employed to examine the profiles of each pair of clones in order to estimate the probability that two clones overlap, and if so, to estimate the degree of overlap. The method has worked extremely well and produced a map of 28 cosmid contigs with surprisingly little effort. This is consistant with expectations for cosmid ordering from a five-fold redundant library. Analogous methods should be applicable to human DNA samples, but the complications that potentially arise from highly-repeated human sequences will have to be dealt with effectively and creatively.

For DNA sequencing, we have been exploring a modified version on sequencing by hybridization (SBH). In one standard design for implementation of SBH, a chip is constructed of all possible 4^n oligonucleotides of length n. The pattern of hybridization of a radiolabeled target to this chip reveals all n-tuple words present in the sequence. This information allows reconstruction of the DNA sequence in the absence of repeats. More complex strategies can be envisioned to reduce the branch point ambiguities caused by repeats. There are two problems with the conventional approach to SBH. First, 4^n is a very large number for $n = 8$ or 9, and the physical chemistry of direct DNA hybridization makes it difficult to work with oligonucleotides shorter than 8. Second, for each perfect match in an oligonucleotide duplex there are three mismatches at each end or a total of six in all. These are thermodynamically almost as stable as the perfect match. Hence the discrimination for a precise sequence target is not as great as one would like.

We have tried to circumvent the two basic difficulties with ordinary SBH by taking advantage of stacking hybridization and the use of sequence-specific DNA enzymes. In our approach the probe is a duplex DNA with a 3' overhanging single strand. Because of the extra thermodynamic stability afforded by the adjacent duplex, such probes need only a five base overhang to provide excellent thermal stability in hybridization. This allows much simpler chips to be used. The target is hybridized to an array of these probes, and then ligated in place. This ensures that the 3' end of the target is read very accurately. Then DNA polymerase is used to extend the original 3' end of the probe to read additional sequence information about the target. This also ensures

that the 5' end of the original target was read correctly. To make this scheme work, in practice, the target molecule must be reduced to a ladder of nested DNA sequences, as in conventional DNA sequencing. However the elements of this ladder do not need to be separated by electrophoresis. Instead they are separated by hybridization and read out in parallel. We are still in the process of optimizing various aspects of this approach, but the initial results are very encouraging. In essence what we have done is to create a strategy that is a hybrid of conventional DNA sequencing and SBH.

Implications

If large scale DNA sequencing becomes a reality, each of us may someday carry around our sequence on a CD ROM, or whatever a decade from now is a convenient form of computer mass storage. The availability of such massive amounts of sequence data raises a number of complex legal and ethical issues. Many of these stem from the fact that, for medical and biological uses of human sequence data, the whole is greater than the sum of the parts. That is, we will be able to use the knowledge most effectively only if we are able to access every one's sequence data and information about their physical and behavioral characteristics. Clearly, the possibilities for invasion of privacy are immense. In order to be able to reap the gains in health care that will stem from the analysis of all this sequence data, we will have to devise very careful measures to protect the rights of individuals. The complexity of this problem should not be underestimated, since each sequence clearly will contain enough information to identify each indvidual even if we try to preserve their anonymity.

Who will have the right to look at an individual's sequence data, and under what circumstances they can excercise this right is only one of a number of serious issues that need to be studied, and, ultimately, managed. Another issue is who owns any commercial rights to individual DNA sequence variations and to related clinical records. The immense problem here is that a DNA abnormality discovered originally in a single individual may ultimately turn out to be useful for the clinical diagnosis of a large number of individuals. Similarly, therapies discovered to be effective for one genetic variant, may be extendable to large numbers of people. We must find a way to distribute the potentially very substantial commercial value of such information fairly between the discoverer, and the source. One extreme view could be a compact among all individuals to share their genetic and related data freely and without charge, for the common good. However, this

may not be satisfactory to those who have labored or will labor hard in the future to discover disease gene alleles.

A great deal of computational analysis will be needed to fully exploit the wealth of DNA sequence data anticipated. This is unlikely to be a serious bottleneck. While the database needed to represent all of human diversity seems very large by current computer standards, the power of computation and the capacity of computer mass storage have been increasing by 10^4 per decade for the last 3 decades. There is no indication this trend is slowing down. Thus, 15 years from now, with a 10^6 increase in computational ability, the information needed to contain the DNA sequenc of the entire human race will correspond to just a few CD ROMs in current technology. Thus there will be no difficulty dealing with data from a computer science view point. The more serious issues are whether we will be able to manage the social and political implications of all of this data.

PREVENTING CONGENITAL DEFECTS: NEW PERSPECTIVES

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Remember,
by knowing about your genes,
you increase your choices,
limit your chances and
safeguard your health.
A. Milunsky, 1989

Molecular basis of inheritance

Human genetics is the biological discipline that studies the diverse aspects of human variability and the transmission of that variability to future generations –inheritance. Its full flowering began in 1953 when Professors James Watson and Francis Crick discovered DNA (deoxyribonucleic acid), what some have called the thread of life, in cell nuclei. Nucleic DNA, whose three-dimensional structure recalls a spiralled double strand –double helix– together with a special type of proteins –protamines or histones– makes up the biochemical skeleton of 46 human chromosomes, 23 of paternal origin and 23 of maternal origin.

Distributed throughout the chromosomes, residing at a fixed position on each chromosome and contiguously joined one to the other, are the genes, the fundamental units of inheritance, numbering between 50,000 and 100,000 in the human species. They may be found as single genes (the great majority), form part of gene families (globin, actin, myosin...), or come grouped together

in gene superfamilies, such as the immunity genes (immunoglobulins, T cell receptors, histocompatible proteins...). Genes, and hence DNA, are in turn made up of chains of biochemical structures known as nucleotides, consisting of a sugar molecule (deoxyribose), a phosphoric acid molecule and a nitrogenous molecule, known as a nucleic base.

Four types of nucleic bases are present in DNA: Adenine, Cytosine, Thymine and Guanine (represented by their initials, A, C, T and G, respectively). When combined in ordered form by means of a given code, the genetic code, discovered by Professors Severo Ochoa and Arthur Kornberg in 1956, the bases form specific genetic messages which permit not only the construction of the protein structure of our bodies, but also the progressive development of all the functions associated with our organism, beginning from the conception of our first cell.

A human DNA molecule consists of approximately 3 billion nucleic base pairs (double spiral) distributed throughout these 46 chromosomes, as already mentioned in preceding paragraphs. While our largest chromosome, chromosome 1, contains around 249 million base pairs, the smallest one, chromosome 21, only has 48 million.

Approximately 90-95% of the DNA contained in the cell nucleus, however, does not code for any type of protein (noncoding DNA). Only around 5% of DNA encodes the various protein types (structural, functional and regulators), that is, expresses some gene. Most of this noncoding DNA separates genes (inter-gene sequences), and a smaller portion of the noncoding DNA is found scattered inside the genes themselves. These are the so-called introns (intervening sequences), gene sequences which separate and are distinguished from the coding gene sequences, or exons (expressed sequences). The function of noncoding DNA is not presently known, though it has been associated with evolutionary mechanisms.

It is necessary to remember that DNA also exists outside the cell nucleus, specifically in the mitochondria, although mitochondrial DNA is governed by a genetic code somewhat different from the code which regulates nucleic DNA. Also, mitochondrial genes primarily code for energy proteins and do not contain much noncoding DNA. They are transmitted by the mother as a result of the specific mechanisms involved in fertilization of the egg by the sperm.

Although the DNA molecule was initially considered to be inalterable, it has been found to be subject to changes or mutations in its biochemical structure. Most of these mutational changes are spontaneous and inexplicable. Nevertheless, certain factors such as chemical agents or ionizing radiation can increase the mutatio-

nal frequency, which in the absence of such environmental factors has been estimated at approximately one mutational change for each 10^9-10^{10} base pairs. Thus, any one of the 50,000 to 100,000 genes comprising the human genome, the average size of which may range from a thousand to several hundreds of thousands of base pairs (there are even some genes made up of more than a million base pairs), may not function correctly, because it is not totally or even partly present, or because of some molecular lesion (point mutation, insertion, inversion...). These alterations can affect one or more nucleic bases and even large chromosome fragments, altering the said gene's genetic message at the DNA level, or in the protein synthesis processes, or in replication, thereby impeding its normally cell function. This cellular dysfunction triggers the appearance of a genetic defect or error.

Congenital defects

In 1982 the World Health Organization (WHO) defined congenital defects as «any anomaly in morphological, structural, functional and/or molecular development, present at birth or with subsequent expression, external or internal, familial or sporadic, hereditary (transmitted to offspring) or not, single or multiple». For many reasons, congenital defects constitute one of the most important categories of human pathology. Approximately 5-6% of all living newborns present some type of congenital defect (chromosome alteration, 1%; monogenic hereditary disease, 1.4%; or congenital malformation, 3%). Their origin may be genetic (genic or chromosomal), environmental, multifactorial (genetic-environmental) or oncogenetic (Table I) in nature.

In developed countries it has been statistically confirmed that nowadays, thanks to improved monitoring of infectious and nutritional diseases, the leading cause (20%) of death within the first year of life is malformations or diseases totally or partly of genetic origin. Congenital defects, in turn, account for roughly 30-40% of all hospital paediatric admissions. In addition, chromosomal or morphological alterations have been found in some 85% of all miscarriages occurring in the first 3 months of gestation, thereby constituting one of the main causes of infertility.

The above epidemiological facts demonstrate the major health consequences of congenital defects and in recent years have led to the development of different health-care programmes combining genetic counselling with early detection, postnatal diagnosis and prenatal testing for the chromosomal, metabolic, molecular, embryopathic and other alterations which can cause psychic or somatic deterioration.

TABLE I
General population incidence of principal congenital defects

	Incidence (live births)
A) Chromosomal alterations,	
Down syndrome (trisomy 21)	1/600-1/700
Edwards syndrome (trisomy 18)	1/3,500
Patau syndrome (trisomy 13)	1/5,000
Klinefelter syndrome (47, XXY)	1/1,000 males
Turner syndrome (45, X)	1/3,500 females
Triple X (47, XXX)	1/1,000 females
B) Monogenic hereditary diseases,	
Dominant	
Huntington's Chorea	1/2,000
Familial hypercholesterolemia	2/1,000
Recessive	
Cystic fibrosis	1/2,000-1/2,500
Phenylketonuria	1/11,000
X-linked	
Duchenne muscular dystrophy	3/10,000 males
Haemophilia A	2/10,000 males
C) Congenital malformations	
Cardiovascular system	40-96/10,000
Limbs	40-80/10,000
Spina bifida	18-50/10,000
Pyloric stenosis	0.3/100

SOURCE: Royal College of Physicians of London, 1989.

Diagnosing congenital defects

1. Neonatal and postnatal screening (carrier detection)

In recent years advances in biotechnological applications to clinical medicine have permitted massive early neonatal diagnosis of individuals affected by certain hereditary diseases (genetic screening). This is possible when the incidence of the disease screened for is high, the technology is accessible (in technical and economic terms), there is easy access to the population to be studied, and effective treatment exists for the disease. This policy of screening newborns which has been adopted in most developed countries is mainly aimed at allowing early treatment of the disorder, thereby avoiding the onset of the mental retardation associated, for example, with phenylketonuria (1/11,000 newborns) or congenital hypothyroidism (1/4,000 newborns).

Other metabolic anomalies for which the World Health Organization has recommended early detection programmes are

hyperphenylalaninemia and «maple syrup» disorder, although the validity of such screening has been questioned for certain cases, such as congenital suprarenal hyperplasia, Duchenne muscular dystrophy, drepanocytosis, or cystic fibrosis, due to the possibility of false positives or negatives, and because there does not yet exist a definitive treatment for many of these pathological processes. Yet, an affected individual's diagnosis through one of these neonatal screening programmes can provide very valuable information to couples as to the potential risk of the recurrence of the pathological condition in a future gestation, which risk should be weighed with the help of genetic counselling.

Also, the development of screening programmes for carriers (postnatal diagnosis) of certain genetic diseases pursues a dual objective: to inform carriers of their specific personal risks and to offer them future options (prenatal diagnosis, adoption, artificial insemination...). Programmes of this type began in the 1970s in certain communities suffering from a higher than normal incidence of certain hereditary diseases due to geographic, religious and/or ethnic reasons. Thus, it can be seen that in some cases the risk of an individual suffering from or being a carrier of a given hereditary disorder may depend in large part on his or her ethnic origin (Tables II and III).

As with neonatal testing, in these cases there should exist minimum requirements for hereditary disease carrier screening: a) exact knowledge of the hereditary pattern; b) complete characterization of the geographic, religious and/or ethnic group at risk with respect to the said disease; c) existence of a quick, effective, simple, automated and economical diagnostic method; d) possibility of prenatal diagnosis. For all these reasons, since postnatal screening (neonatal-carriers) is focused on preventing genetic pathological conditions, its future is clearly tied to the development of the Human Genome Project, given that the number of genetic diseases which can be detected early is steadily increasing thanks to progressive gene characterization and identification.

TABLE II
Incidence of certain hereditary diseases different ethnic and geographic groups

Hereditary disease	Incidence (live births)
Drepanocytosis (Black American population)	1/400
Drepanocytosis (Black African population)	1/40
Thalassaemia (Black population)	8/1,000
Thalassaemia (Greece-Italy)	1/400
Cystic fibrosis (Caucasian population)	1/2,500
Tay-Sachs (Ashkenazim)	1/3,600
Familial Mediterranean Fever (Sephardim)	1/8,000

SOURCE: Choices, Not Changes. A. Milunsky, 1987.

TABLE III
Incidence of individual carriers of certain hereditary diseases in different ethnic and geographic groups

Hereditary disease	Incidence (carriers)
Drepanocytosis (Black population)	1/12
Cystic fibrosis (Caucasian population)	1/25
Phenylketonuria (Caucasian population)	1/80
Tay-Sachs (Ashkenazim)	1/30
Porphyria (S. African Caucasian population)	1/330
Thalassaemia (Greece-Italy)	1/10

SOURCE: Choices, Not Changes. A. Milunsky. 1987.

2. *Prenatal diagnosis*

Unfortunately, at present only in a very few cases is there effective therapy (surgery, pharmacology...) for most congenital defects. Since no pregnancy is exempt from genetic risks, prenatal diagnosis is seen as one of the options available to a couple within a programme of pregestation, prenatal and/or postnatal genetic counselling, not just due to the risk of recurrence in couples with a previously affected child, but to the innate risk to which all individuals are exposed of having a child with congenital defects.

Given the different types of genetic counselling and their common characteristics (confidential, non-coercive, clear, concise, objective, and respectful of the family's decision and autonomy), families can receive complete information to aid them in assimilating and comprehending the different aspects of the disease or purpose of the genetic consultation (nature and prognosis of the congenital defect, risk and recurrence, diagnostic techniques and possibilities, testing reliability, options...).

In general terms the basic strategy of prenatal diagnosis initially consists of establishing risk groups by identifying those individuals and/or couples with a higher than normal genetic risk. In addition to including innocuous, simple, reproducible and inexpensive diagnostic methods, this level of screening should offer a high level of discrimination and low rate of false positives. Of fundamental importance are a series of selection criteria that allow the greatest risk cases to be discerned (Table IV). These selection criteria should also allow the individuals and/or couples seeking counselling to be grouped into three distinct categories according to their overall theoretical risk of having offspring affected by a genetic defect.

a) LOW RISK (< o = 1/100)

– Woman 38 years of age or younger

- Couples with an earlier child affected by a simple trisomy (trisomy 21, trisomy 18, trisomy 13...)
- Couples with a direct family member having a Neural Tube Defect (NTD)

b) MODERATE RISK (1/20-1/100)

- Woman 39 years of age or older
- Father carrier of a translocation (D/G or G/G chromosomal groups)
- Earlier child with a NTD
- One of the progenitors has a corrected spina bifida

c) HIGH RISK (1/20 or greater)

- Woman 40 years of age or greater
- Both progenitors are carriers of an autosomal recessive inheritance disorder
- One of the progenitors is affected by an autosomal dominant inheritance disorder
- Mother carrier of an X-linked inheritance disease
- Couples with two or more earlier children affected by a NTD
- Mother carrier of a translocation (D/G or G/G chromosomal groups)
- Both progenitors are balanced carriers of a chromosomal abnormality (deletion-insertion)

TABLE IV
Principal selection criteria for primary detection in persons, couples or groups with high risk of presenting a congenital defect

– Positive family history (earlier child and/or family antecedents)
– Repeated miscarriages
– Progenitor age
– Viral infections (chickenpox
– Ethnic-geographic-religious background (thalassaemia, Tay-Sachs, NTD[1]..)
– Maternal diabetes
– Rh- group
– Abnormal AFPMS[2] values
– Positive echograph exploration
– Progenitor carrier of chromosomal abnormality
– Progenitor carrier of hereditary disease
– Potential teratogenic factors (radiation, alcohol, drugs...)
– Consanguinity

[1] NTD: Neural Tube Defect
[2] AFPMS: Alpha-fetoprotein in maternal serum

Although selection criteria and risk groups allow screening for genetic defects in general, the ultimate diagnostic strategies to be

pursued will obviously depend on the specific type of congenital defect to be detected.

A) Risk of chromosomal alterations

a) Progenitor age. It has been scientifically observed that the appearance of certain chromosomal alterations (trisomy 13, trisomy 18, triple X and Klinefelter syndrome) display a correlation with advanced maternal age (= o 35 years). This correlation is most pronounced in Down syndrome (trisomy 21) (Table V).

Similarly, Danish statistics have shown that a woman below the age of 35 whose partner is 55 years or older has a 1% risk of bearing children with a chromosomal abnormality.

TABLE V
Incidence of Down syndrome and chromosomal abnormalities (total) in amniocentesis (+/–15-16th gestation week)

Mother's age (years)	Down Syndrome (trisomy 21)	Total chromosomal abnormalities
33	1/417	1/185
34	1/323	1/154
35	1/250	1/125
36	1/192	1/101
37	1/149	1/82
38	1/115	1/66
39	1/89	1/53
40	1/69	1/42
42	1/42	1/27
44	1/25	1/17
46	1/15	1/10
48	1/9	1/6

SOURCE: E. Hook. Albany Medical College. New York.

b) Progenitor carrier of a chromosomal abnormality. Statistically speaking, 1/500 individuals are carriers of a frequently transmissible chromosomal abnormality. Although general screening for chromosomal abnormalities is practically impossible to carry out for a number of reasons (number of individuals to be studied, economic cost...), in order to detect such abnormalities it is advisable for a karyotype (chromosome study) to be carried out when there exists a clinical suspicion that one of the parents has a specific chromosomal disorder, either because of a positive family history (earlier affected child or family antecedents), repeated miscarriages, and/or infertility.

If the detected chromosomal abnormality is a translocation or mosaicism, then both parents should be studied

to determine the origin of the disorder. Once this has been discovered, the affected family pedigree (paternal or maternal) should be studied in order to permit detection of other carriers.

c) *Earlier child with a chromosomal abnormality.* Couples with a previous child affected by a chromosomal pathological condition have a variable degree of recurrence of the same, depending on the type of cytogenetic anomaly and chromosomes involved. Hence their classification in this specific risk group.

d) *Chromosomal abnormality biochemical markers.* In certain types of chromosomal disorders, particularly with Down Syndrome, a pronounced correlation has been observed for a certain gestation age between the presence of the abnormality and low AFP (alpha-fetoprotein) and unconjugated oestriol levels in maternal serum, as well as high values of the human chorionic gonadotrophin β fraction in maternal serum.

B) Risk of hereditary disease

In this case, the basic strategy to be followed is the diagnosis of carriers of the hereditary disease to be detected, if possible by means of a pregestation study (prospective analysis). However, the main limiting factor in this carrier screening is the inheritance mode (dominant, recessive and X-linked) of the more than 5,000 hereditary diseases thus far described (Mendelian inheritance in man, V.A. McKusick 1992). Thanks to molecular biology techniques, we are seeing a gradual increase in the number of pathological entities which can be detected (Table VI).

Thus, while it is currently possible to detect individual carriers of certain hereditary diseases on the basis of a positive family history (Duchenne muscular dystrophy, haemophilia...), carrier screening for the entire population can only be offered for haemoglobin diseases and Tay-Sachs disease. This is difficult ground. For example, although isolation of the cystic fibrosis gene in later 1989 led many to think that it would be possible to carry out systematic population-wide screening for cystic fibrosis carriers, certain factors, such as the great mutational heterogeneity presented by said gene in different caucasian populations, in most cases currently limits the detection of carriers to the families of the affected person.

C) Risk of congenital malformations

a) Given that the chickenpox virus is one of the leading infectious causes of congenital malformations, a priority concern must be attaining maternal immunity prior to pregnancy in order to avoid such malformations.

TABLE VI
Hereditary diseases diagnosable by means of molecular biology techniques (J.D. Goldberg, 1990)

Defect	Inheritance	Chromosome
Alpha-antitrypsin deficiency	AR	14
Alpha-thalassaemia	AR	16
Polycystic kidney disease in adult (Type I)	AD	16
Thalassaemia-β	AR	11
Congenital adrenal hyperplasia	AR	6
Cystic fibrosis	AR	7
Duchenne-Becker muscular dystrophy	LXR	X
Alzheimer's disease (familial)	AD	21
Familial hypercholesterolemia	AD	19
Familial colon polyposis	AD	5
Fragile X syndrome	LXR	X
Gardner syndrome	AD	5
Haemoglobin Sc	AR	11
Haemophilia A	LXR	X
Haemophilia B	LXR	X
Huntington disease	AD	4
Multiple endocrine neoplasia type I	AD	11
Multiple endocrine neoplasia type IIa	AD	10
Myotonic dystrophy	AD	19
Neurofibromatosis type I	AD	17
Neurofibromatosis type II	AD	22
Norrie disease	LXR	X
Transcarbamoylase ornithine deficiency	LXR	X
Phenylketonuria	AR	12
Retinoblastoma	AD	13
Falciform anaemia	AR	11
Tay-Sachs disease	AR	5
Von Hippel-Lindau syndrome	AD	3
Wiskott-Aldrich syndrome	LXR	X

AR: Autosomal recessive; AD: Autosomal Dominant; XLR: X-Linked Recessive

b) Detection in the 16th-18th gestation weeks of high levels (greater than percentile 95-97) of alpha-fetoprotein in maternal serum (AFPMS), which is the case in 3-5% of pregnant women, in some cases may serve as an indirect indicator of the possible existence of a Neural Tube Defect (NTD). Such situations therefore warrant high-resolution echography. If no congenital defect is observed, amniocentesis may be performed to evaluate the AFP level in the amniotic fluid (AFPAF), a high value for which would indicate the very likely presence of spina bifida.

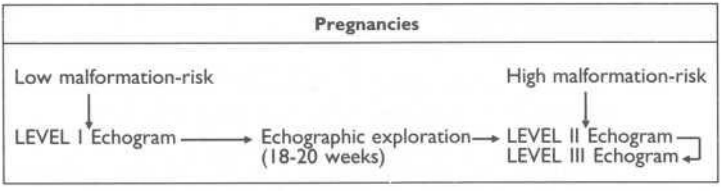
High AFPAF values, however, could also be due to incorrect closure of the abdominal wall (omphalocele) or abnormal filtration via the kidneys (congenital nephrosis). For this reason, and in order to precisely determine the origin of the loss or filtration of the fetal AFP found in the amniotic fluid, a characteristic central nervous system enzyme, acetylcholinesterase, is also evaluated. The presence of this enzyme, in the absence of conta-

mination with fetal blood, allows 90% of these diagnostic doubts to be resolved. Statistics demonstrate that the level of NTD detection in 100,000 monitored pregnancies, thanks to the combined action of AFPMS-AFPAF and high-resolution echography, allowed diagnosis of more than 99% of such congenital disorders (80-90% of spina bifida and approximately 100% of anencephalies).

Fortunately, although the vast majority of pregnant women with high AFPMS levels subsequently display normal echograms and AFPAF levels, they have been found, at the Human Genetics Center of Boston University, to have a higher proportion of high-risk pregnancies (fetal deaths, stillborns, premature births...), thereby permitting the use of this early detection method to assure better followup and monitoring of such pregnancies.

c) No doubt the most effective detection method for congenital malformations, whether in families with antecedents or in those with a clinical suspicion of possible malformative processes (maternal diabetes...) (Figure 1), is an evaluation of the state of the fetus by means of basic, high-resolution echography at different points in the pregnancy.

FIGURE 1
Echographic diagnostic strategy for congenital malformations (J.M. Carrera, 1992)



2.1 Prenatal Diagnosis Techniques

Prenatal diagnostic techniques or strategies for congenital diseases may be classified into two main groups: invasive and non-invasive.

A) Non-invasive techniques

a) Echography-Ultrasonography. Allows fetus to be viewed by means of ultrasound and involves no danger to mother or fetus, permitting diagnosis of a large number of congenital malformations (Table VII).

TABLE VII
Principal congenital malformations detected by echography-sonography (J.M. Connor and M.A. Ferguson-Smith, 1991)

– **Central Nervous System** Anencephaly, spina bifida, hydrocephaly, microcephaly, encephalocele.,
– **Limbs** Polydactilism, imperfect osteogenesis, shortening and deformation of limbs
– **Heart** Severe cardia defects
– **Kidney** Renal agenesis, renal polycystic disease
– **Gastrointestinal tract** Duodenal atresia, back abdominal wall defect, diaphragmatic hernia

b) *Radiography.* Only used in the prenatal diagnosis of certain bone disorders, such as skeletal dysplasia and osteoporosis, optimally observable in the 20th week of pregnancy.

c) *Prenatal biochemical markers for chromosomal disorders and Neural Tube Defects (NTD).* Evaluation in mother's serum at a specific gestation age of certain biochemical markers which in determined cases may indicate certain pathologies.

B) Invasive techniques

Unlike the foregoing techniques, the methods required for carrying out these techniques involve certain risks to the mother and/or fetus (Table VIII).

a) *Chorionic villus sampling (CVS).* Involves transabdominal or transcervical chorionic villus sampling (identical genetic makeup as the fetus) under echographic control without the need for anaesthesia at a gestation age averaging from between 8 to 12 weeks. Each biopsy specimen provides approximately 15 to 20 mg of chorionic villi, which are used to determine fetal sex and karyotype, and for biochemical and molecular studies. Owing to the early stage at which this technique is employed, the risk of fetal loss (2-4%) is greater than with amniocentesis (0.5-1%), although the risk of infection is low (1-3/1,000). In recent years there has been a trend toward transabdominal rather than transcervical extraction, primarily owing to the lower risk of fetal loss. Some centres have conducted very early chorial biopsies (prior to 9 weeks gestation).

b) *Amniocentesis.* Amniocentesis involves transabdominal withdrawal, in aseptic conditions and under strict echographic control of fetal and placental location, of a certain volume of amniotic fluid (AF) from the amniotic sac (risk of infection: 1/1,000).

While this technique is usually applied at around 15-16 weeks gestation, when the ratio of viable to non-viable fetal cells in the amniotic fluid is at its highest, it may also be used earlier: ultra-early amniocentesis (prior to 15 weeks gestation). The fetal cells found in the amniotic fluid come to be there as a result of having been sloughed off from the fetus' skin, gastrointestinal tract or urinary system. The amniotic fluid thus extracted (10-20 ml) is used for certain analyses (fetal sex, karyotype, biochemical assays, evaluation of AFPAF, and molecular studies) which, in different testing conditions (cell culture, DNA extraction, enzyme quantification...) allow a possible genetic defect to be diagnosed. Less aggressive techniques are currently in development which will also require smaller samples (microfiltration of a minimum volume of amniotic fluid).

c) *Fetoscopy.* This technique permits viewing of the fetus by means of an endoscope or fetoscope inserted in the uterus through the abdominal wall, accompanied by anaesthesia and echographic control.

This allows withdrawal beyond the 17th gestation week of fetal blood, skin or tissue for diagnosis or diagnostic confirmation of diseases such as hereditary haemolytic anaemias, certain immune and chromosome mosaic disorders.

d) *Funiculocentesis.* This technique is also used to obtain, under echographic control, fetal blood by means of puncturing the umbilical cord (placental insertion) through the outer abdominal wall. Most funiculocenteses are performed beginning at the 20th gestation week, although some cases have been reported during the first trimester (β-thalassemias), both cases requiring prior confirmation of the exact origin of the blood (mother or fetus). Fetal blood is mainly used for a diagnostic confirmation, late diagnosis or for the study of certain types of infection or blood disorders. Nowadays, funiculocentesis is an alternative fetal blood sampling method to fetoscopy.

TABLE VIII
Main risks associated with invasive prenatal diagnostic methods

CVS	Amniocentesis	Fetoscopy	Funiculocentesis
Embryo death	Loss of fetus	Premature birth	Infection
Miscarriage	Fetal lesions	Haemorrhaging	Premature birth
Intrauterine infection	Fetal infection	Infection	Loss of fetus
Rh isoimmunization	Maternal death	Loss of AF	
Fetal malformation	Maternal haemorrhaging	Maternal lesion	
Amniotic bands	Uterine contractions	Fetal lesion	
Premature birth	Maternal infection	Placental lesion	
Detached placenta	Perforation of viscera		
Ruptured membranes	Rh isoimmunization		
Placenta previa and accreta			
Loss of AF			

AF: Amniotic Fluid
SOURCE: *Prenatal Diagnosis.* J.M. Carrera, 1987.

2.2 Outlook for Prenatal Diagnosis

In recent years, thanks to steady improvement in techniques and methods permitting greater access to the fetus and to the ever more knowledgeable multidisciplinary teams (echographers, cytogeneticists, obstetricians, biochemists, molecular biologists...) working in this field, prenatal diagnosis has improved the detection of congenital defects to a degree that could not have been originally imagined.

Thus, the combined use, on the one hand, of invasive diagnostic techniques that permit fetal material to be withdrawn at different stages of the pregnancy (chorionic villus sampling, amniocentesis, funiculocentesis, fetoscopy) and its subsequent analysis using cytogenetic, biochemical-metabolic, and/or molecular techniques, and, on the other, non-invasive diagnostic techniques (ultrasound and echography –digital technique, grey scaling, biometry, vaginal probes, real time, Doppler–, biochemical and/or echographic markers...), now allows prenatal diagnosis of more than 600 different types of congenital defects (*Catalog of Prenatally Diagnosed Conditions,* D.D. Weaver, 1992).

Nevertheless, diagnostic capacity is not uniform for the different types of congenital defects (Table IX).

TABLE IX
Prenatal diagnostic capacity

Type of congenital defect	Theoretical prenatal diagnosis capacity (%)
Chromosome disorders	100
Neural tube defects	>95
Dysmorphism	>90
Congenital metabolism errors	<20
Haemoglobinopathies	>90
X-linked recessive diseases	20 (100 depending on sex)

SOURCE: *Prenatal Diagnosis.* J.M. Carrera, 1987.

In the coming years radical advances may be expected in the prenatal diagnosis of congenital defects, thanks to modifications of certain types of procedures (earlier and quicker studies...), use of new diagnostic techniques (*in situ* hybridization, ligase chain reaction, flow cytometry, biochemical markers for NTDs and chromosomal abnormalities...), development of new methods (preimplantation diagnosis, analysis of fetal cells in maternal blood, echographic markers for chromosome disorders...), improved training of specialists, greater coordination and organization of different health care levels.

Conclusions

The unfolding of the different stages making up the scientific, technical and human challenge of the Human Genome Project will revolutionize our basic knowledge of monogenic diseases and, what is more, serve to reveal the mechanisms and processes involved in hereditary problems of other types (polygenic, multifactorial...). This will provide ever greater benefits for prenatal and postnatal diagnosis, widening their diagnostic possibilities (presymptomatic, preimplantation...). This expanding knowledge of the secrets zealously guarded within the human genome will sooner or later allow us to know the origins and regulation of oncological or immunological processes.

Lastly, the hopes and intellectual and technological effort deposited in this project should allow treatment of disease at the molecular level, that is, gene therapy. Nevertheless, all this scientific, technological and methodological development accompanying the Human Genome Project gives rise to a series of ethical, legal and social problems, questions and considerations which will oblige serious reflection and the development of an ethical and legal code to avert possible transgression of the innate rights of all human beings.

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LAW AND THE HUMAN GENOME PROJECT

Andreas Klepsch

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I will try to give a contribution to the subject state of the art from the point of view of somebody involved in developing and managing research programmes in the European Communities.

I could report on the strategy of the projects we are going to support and report on what we are going to do in the next round of programs –mini-projects we envisage for a period of 2-2.5 years starting as of now. So when we got to, say, the mid-1980s, the time was apparently right for a coordinated effort on sequencing projects, genome projects in general. Among those of course was the Human Genome Project. I think that was a dramatic change in the mid-1980s: sequencing or systematic mapping not for purposes of detecting specific gene-related diseases, but to go for a coordinated effort to map the genome as a whole. To give you an idea of the task, this would require a 72 metre stack of paper just to describe the sequence of the human genome. I think nobody, even with the right equipment, would be able to handle this kind of information even if it just fell from heaven.

As I said, the time to make an approach was right, in the mid-1980s in the US and the EEC. Programmes, projects which had in mind genome research started in the late 1980s, early 1990s. We had avoided the discussion, also mentioned by Dr Cook-Dee-

gan, over whether it is more biotechnology or more medicine and so on, by giving the human genome its own identity from the outset. We had an independent programme dealing exclusively with the human genome, located in the unit that normally deals with medical research. We had four or five major tasks: to improve the genetic map and obtain a physical mapping, to do something for data handling and databases, and to improve methods and methodology for applications in medicine. We structured the programmes so as to make the sources available to European researchers. Thus, we supported the distribution of YAC clones, cDNAs, costs and many other things, on the condition that there be free access for European scientists to those resources and there be a certain exchange of information, feedback, once one's clones were mapped, map sequences were submitted and so forth.

Early on it was realized that to do something that in the mind of many people dealt directly with creation had many implications. Earlier this morning we heard a lot about the ethical considerations. My colleague Dr Elizalde will report in more detail about the ethical social and legal aspects this afternoon in the session in which he is scheduled to take part. We not only acknowledged these when we drafted the programme, however. Utmost consideration had to be given to ethical considerations. We even restricted our research, made certain amendments to the contacts, conducted a systematic ethical review of all projects, and excluded certain kinds of research from the programme objectives. This was done at all level levels, but for financial reasons gene therapy of any kind was excluded. A working group was established on the ethical, legal and social aspects. As mentioned earlier, we have already published a first report and have received results of 18 studies commissioned by us. We are going to publish and review those studies and then reconvene the group, called ESLA, to prepare a second or final report concerning this programme.

Just recently we had the deadline of this call for proposals in January. We launched a new call for proposals with a much higher budget (23 million for research) as part of the biomedical research programme, maintaining the identity of the specialized effort on the human genome, by means of special contract provisions, special funding channels, and many other means. We will cover the following areas: we will again work to improve the genetic map, go on to physical mapping, DNA sequencing, do more on data handling and databases, technology development and look for applications. The official decision about the funding has not yet been made, but I think it is already possible to report some trends that will maintain a strong emphasis on infrastructure. However, although the funds have nearly doubled, the in-

crease in the resources is much lower in relation to the whole programme. That means we have more money for, say, freelance projects on these subjects. We are going to have highly interesting projects on data handling and databases. We are currently discussing what we are going to do in the next programme. There is some guesswork that needs to be done and we know something about technology development what we will take into account. But we do not know which of the techniques developed will fulfil their promise in 2 or 3 years and what additional options will exist. We cannot make predictions. In the past, 2 years ago, when we discussed what we were going to do now, it was the scientists who advised us to keep the areas of genetic linkage mapping and physical mapping separate. I would now say that this was a mistake. Now we are trying to turn these projects into something that I would call integrated mapping. I do not see that the projects themselves justify a separation between the different types of mapping which was defended in the past, including sequencing methods.

We are also discussing what we are going to do in the future with respect to sequencing. The basic strategy more or less developed 5 years ago was to use different systems of mapping to have the sequences, clones, and subclones ready for sequencing, and to sequence those parts of interest. There is now so much material around, there is so much technology development and we expect so much improvement in the field of data handling, databases, new software development, that I think the question must be asked as to whether going directly to sequencing makes much sense any more, at least in 2 years, or maybe immediately now. What I mean is, we started on the human genome based on this cascade strategy of ever finer results to arrive at the sequence and to use and exploit the knowledge of the sequence. At the same time we had colleagues in the biotechnology programme who are sequencing a yeast genome by just sequencing the yeast genome from chromosomes of yeast from one end to another. And they have done that successfully on chromosome 3. Currently, a number of other chromosomes are under investigation. But what is really different between an organism like yeast and the human genome is that it takes very little effort to find genes from the food sequence of yeast, or at least to find open reading frames of a certain length. From there you have the hot spots where you can assume there will be a gene, find those genes, find the expression of those genes and then go on to a functional analysis. That is not the case with the human genome, because the human genome is organized in such small gene portions –with exons and introns– that you will virtually find nothing. Also, you have long strands in between where there are no genes at all. I think the figures are still right, but we cannot handle or we have no sound idea for more than 90% of the human DNA,

including controlling regions which we just assume are there to keep a certain distance. So I believe we will have to reconsider the integration of the different genome projects, maintaining the identity of, for example, medical applications, and not get involved with reading problems. I think we have to consider not only data handling and data management, but also a totally new approach or access to the human genome from the field of informatics, computer science. We need some algorithms which help us to find genes to which to attribute new functions and then identify functions from this information. And, last but not least, and something I have not emphasized because two of my colleagues will be speaking on this subject, there are the ethical considerations or the ethical, social and legal aspects of this work and its implications. And I would stress the implications of the work, rather than the work itself, as needing further consideration. This has to be strengthened in research programmes.

RAPID HUMAN GENE DISCOVERY: IMPACT ON SCIENTIFIC AND SOCIAL CHANGE

J. Craig Venter

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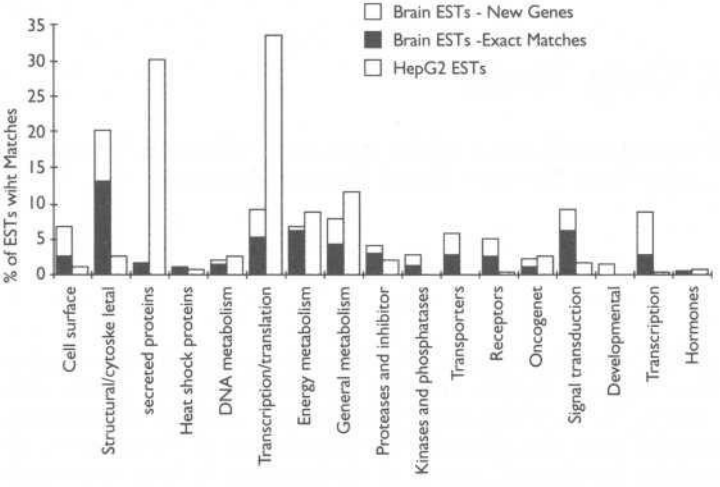
In 1990, our laboratory at the National Institute for Neurological Disorders and Stroke, National Institutes of Health (NIH), was working on two large-scale pilot genome projects to sequence cosmids from the myotonic dystrophy region of chromosome 19 and the Huntington's region of chromosome 4. Frustration with the long, slow process of sequencing and analyzing the more than 200,000 base pairs of genomic DNA, only to discover that cDNA sequence information was absolutely needed for its interpretation, ultimately led to the decision to isolate and sequence short cDNA clones that would uniquely and effectively identify genes (Venter *et al.*, 1992). In mid-1991, we published a paper in *Science* (Adams *et al.*, 1991) describing over 300 new human genes identified by expressed sequence tag (EST) sequencing.

Although cDNA sequencing had been used for several years to analyze genes, the EST sequencing method constituted a strategic breakthrough for gene discovery by increasing the rate of discovery by 100 to 1000 fold. EST sequencing is also cost effective. From the estimated cost of $5.00-$15.00 per finished base pair at the initiation of the Human Genome Project, our technique of single-pass EST sequencing has reduced the cost of identifying genes to less than $0.12 per base pair. Recognizing these improvements, laboratories in North America, Europe and Japan have

rapidly turned to EST sequencing as the focus of their genome efforts.

Beginning with our first results from the EST method in 1991, we have published EST sequences from over 8,500 human genes and made the sequence data and computer analysis results available to the community via a computer database (Adams *et al.*,1991; 1992; in press). All cDNA clones from our project are available to the world scientific community from the American Type Culture Collection.

FIGURE 1
Functional categories of ESTs with database matches



Large numbers of new human receptors and transporters have been identified; all of these are immediate candidates for further investigation as targets for specific drug development. We are proceeding to characterize selected protein products of these new genes biochemically and pharmacologically. We have also identified many new transcription, translation and splicing factors, structural proteins, enzymes and cell-surface proteins. As these genes are further characterized, we expect that many will prove to be of medical interest.

By sequencing ESTs from cDNA libraries constructed from many different tissues, we can construct expression profiles for many human genes simultaneously. Figure 1 compares the numbers of genes from several different functional categories that have been identified by EST sequencing from brain (Adams *et al.*, 1991; 1992; in press) and HepG2 hepatocytes (Okubo *et al.*, 1992). Over 140 human cDNA libraries are currently being sequenced at The Institute for Genomic Research (TIGR). These data will allow us to systematically compare the levels of expression of thousands of

genes across tissues and developmental stages. We will be able, for example, to identify genes that are expressed specifically in pre cancerous or metastatic tumor cells (Figure 2, p. 144), and use this information for early diagnosis of cancers.

TIGR scientists have also developed novel software for streamlining the quality control, analysis, and management of EST data (Kerlavage *et al.*, 1993; White *et al.*, 1993). This software has now been adopted by several other high-throughput sequencing labs. TIGR is currently developing the world's first gene expression and function database, which will be available to the world scientific community via international computer networks.

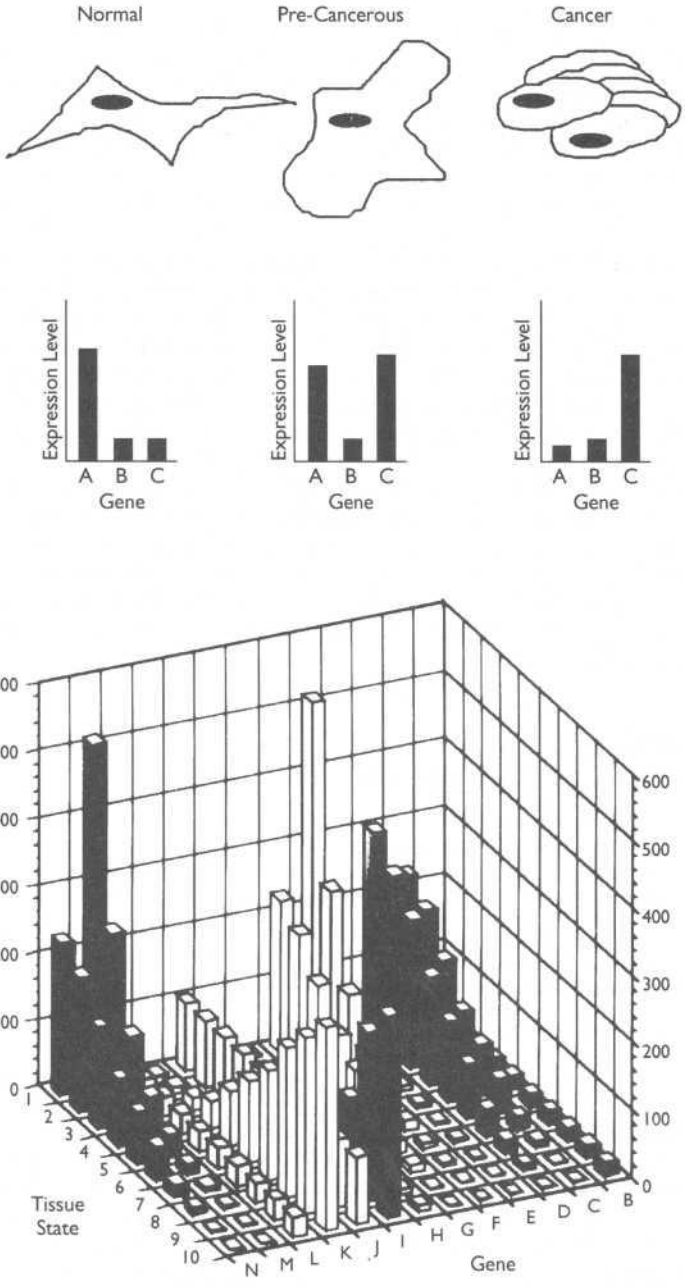
Through cDNA sequencing, we are approaching the goal of sequencing the majority of human genes much more rapidly than originally anticipated. This means that the scientific, social, legal and ethical issues will be likewise accelerated. The Institute for Genomic Research believes that scientific progress must be guided by ethical and legal principles; therefore, we have formed a Department of Research Policy and Ethics, chaired by Leslie A. Platt, J.D., to encourage public examination of current and emerging genomic issues (Table 1).The Research Policy and Ethics Department has instituted a multi-faceted program to be developed and coordinated in close consultation with a research policy and ethics advisory council. Council membership reflects a broad and diverse spectrum of scientific and lay leaders. The goal of this effort will be to help inform and guide essential public discussion about the implications and impact that modern genome research will have on the world.

TABLE 1
Current and Emerging Genomic Issues

- Gene patenting
- Societal uses of genomic information
- Implications of genetic testing
- Genetic knowledge and reproductive choices
- Confidentiality and access to life/health insurance
- Implications of genetic experimentation
- Effects on American/world healthcare systems
- Challenges to religious and philosophical views
- Approaches for maximizing advances from genomic research while recognizing and addressing risks.

A second critical purpose of this effort will be to assure the integration of an empirical examination, from the outset, of the ethical basis for the genomic research conducted at TIGR. TIGR believes that we will thereby be better able to fulfill our own moral responsibility, as well as to provide a template for others engaged in basic or applied genomic research, to integrate serious exploration of critical research with the underlying scientific work.

FIGURE 2
Fallocoing gene expression through physiclogical and pathological changes



The original Human Genome Project plan envisaged sequencing all human genes by 2005; The Institute for Genomic Research anticipates identifying the vast majority of human genes within the next 2 years. The knowledge gained from this research will revolutionize medicine, agriculture and biotechnology; therefore, we must be prepared to use this knowledge wisely.

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STATE OF THE ART

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(The opinions expressed are those of the author and do not necessarily reflect the views of the Depart of the Army, Department of Defense, or the United States goverment.)

I will comment on the technology of the Genome Project as an outsider. I will make the point, as others have before me, that we will see an accelerated pace in scientific progress.

Technology development was and is a significant part of the genome initiative. A goal of the first 5 years is the improvement in the efficiency and cost effectiveness of mapping and sequencing technologies; including the reduction in the cost of sequencing to $0.50 per base.

Much of the progress in the Genome Project thus far has come from simply robotizing manual steps or technologic breakthroughs in other than DNA sequencing itself. Major advances came with new strategies for directing mapping and sequencing efforts. The polymerase chain reaction, coming to the fore as the project was starting, and YAC cloning could be considered merely as examples of sample manipulation. But the Human Genome Project has not yet produced major sequencing technology breakthroughs. If and when these sequencing breakthroughs occur, progress will quicken.

The first commercial sequencer preceded the advent of the Human Genome Project. Several automated DNA sequencers now exist on the market. In fact, more than 1,000 instruments have been sold worldwide at a cost of approximately $120 million. Commercially available automated sequencers when run in efficient large-scale operations can achieve sequencing at below $1.00/base, near the realm of the 5 year stated goal of $0.50 per base. This recognition, that current automated sequencers were better than originally thought, perhaps de-emphasized focus on incremental progress in sequencing in favor of longer term research. Significant funds have been expended on advanced technologies, but they are still in progress. The incremental progress that has been made and is on-going has generally been through the efforts of the commercial manufacturers themselves. Thus, the great progress in the Human Genome Project to date has been made without the benefit of major technologic breakthroughs in automated sequencing. Nonetheless, several areas into sequencing technology may soon bear fruit.

Current automated instruments save time primarily by elimination of autoradiography, by automating the analysis, and by permitting a consistent work flow. Electrophoretic run times are longer than with manual sequencing, typically 8 to 12 hours, because the entire set of bands must move past a detector. Other than gel fabrication and set-up, it is this electrophoretic run time that is the limiting factor, for the slow turn-around-time of conventional automated sequencers. The electrophoretic run time is dependent on the voltage applied across the gel. The greater the voltage, the faster the run. However, the voltage which can be applied is limited by the generation of heat. Conventional polyacrylamide slab gels are run from 1,000 to 2,000 volts (approximately 40 V/cm).

But, less is more. Ultrathin gels have a smaller cross-sectional area and carry less total current. Thus ultrathin gels can tolerate greater voltages before being limited by Joule heat generation. One manual system on the market claims electrophoretic run times of 15 to 30 minutes. The ultrathin gel measures 0.05 mm in thickness and is usually run at about 6,000 volts (100-200 V/cm). Ultrathin gels also have greater resolving power and thus are capable of accurately determining a greater number of bases per run. For instance, one purveyor of ultrathin systems claims 77% more bases in one fifth of the time of conventional sequencing gels.

But, less is more. Rather than performing electrophoresis on a planar slab gel, electrophoresis can be carried out in a capillary with an internal diameter of 50 to 75 microns. These capillaries

dissipate heat more efficiently than slab gels and thus can tolerate still higher voltages.

Capillary gel electrophoresis (CGE), in which the capillary is filled with a polyacrylamide gel matrix, is an excellent method for sequencing DNA fragments. CGE is generally run at 8 to 15 kV (150-300 V/cm) with a real time analysis of 20 to 40 minutes. Instead of a gel, a noncrosslinked polymer matrix can be used and run times one third of the CGE can be achieved.

The greatest time is saved not in the run time, but in the elimination of fabrication and set-up of a polyacrylamide gel. The capillaries are purchased pre-filled and are used repeatedly. Thus, CGE can be a truly automated system. Samples are loaded onto a sample autoloader and the operator can walk away.

However, the per run advantage in speed of current CE instruments is negated by the fact that they are single channel whereas there are many lanes on a slab gel instrument. Multichannel CEs have been described. Furthermore, the CE can be operated in a multiwavelength fluorescent mode. The potential clearly exists to replace current automated sequencers with CE-based instruments.

As with ultrathin gels, the smaller channel size results in greater resolution, which translates into higher base calling rates. Some have claimed reliable sequences to beyond 800 bases using CGE.

A CE instrument, suitable for DNA typing, costs one third the price of some automated sequencers. The per run cost is less and the small volumes required translate into a reduction in reagent costs.

We have seen that smaller electrophoretic channels translate into less heat generation, greater voltage tolerance, and decreased run times, as well as increased resolution and decreased cost. One can imagine the potential of further miniaturization through current microfabrication techniques. The microchip revolutionized the electronics industry and could theoretically provide the same for this area. For instance, it is possible to fabricate an array of still smaller capillary electrophoretic channels etched in a silica chip. A major initiative has been launched using the microchip technology in another way; specifically, direct sequencing by hybridization because thousands of possible combinations of solid phase oligonucleotide probes can be efficiently manufactured in the same way that thousands of transistors are packed into an integrated circuit chip.

But, less is more. Precisely because mass spectrometry (MS) analyses individual molecules, it can perform analyses in seconds

or less with atomic scale resolution. Accordingly, MS may hold the greatest potential for DNA sequencing. Although many potential strategies can be theorized for MS sequencing, in the simplest form MS, like electrophoresis, is merely a method to separate DNA fragments by size (mass). There has been a revolution in the ability of mass spectrometers to analyze large biomolecules, however, current efforts for MS sequencing are not at hand.

While dramatic advances in DNA sequencing technology have been late in coming, they will arrive. I believe, although this view is not shared by all, that we are about to see a revolution in sequencing technologies. I predict that within the next few years we will see commercial instruments of greatly increased throughput based on nonslab gel technologies. Because there are other research and commerical interests, this technology will be developed despite the Genome Project itself. With these advances in sequencing technologies, the development of genetic information will further accelerate. The impact will be far beyond the Human Genome Project itself, but to all biological sciences and clinical medicine. The ethical, legal, and social implications will grow accordingly.

Acknowledgement: I thank Alison Tinsley for editorial help in preparation of this manuscript.

ROUND TABLE

ROUND TABLE

Hamilton O. Smith. I don't know which one of the panellists I should address this to. Last year what some consider a technical breakthrough in sequencing using hexamer primers was announced. What is your opinion of this method in terms of speeding up sequencing, and is it a reality at this point?

Answer. What you are referring to is the ability to pre-synthesize all the random hexamers and then to pull them out of a pre-existing library to speed up sequencing, where the assumption is that synthesis of oligonucleotides is really an important step. It is not highly likely that this is going to have an impact on human genome sequencing, because of all the repetitive elements in the human, but it could have a dramatic effect on the full length sequencing of cDNAs.

Question. In order to ask the question I need to have Mr Venter confirm, above all, if he was the person behind the human gene patent applications filed in the United States and with the European Patent Office. Then, the truth is that although the subject might be discussed tomorrow, I do not want to pass up this opportunity to ask him, if he was the person, to give us a little bit of an explanation as to the justification, in his view, of this policy of patenting human genes.

Craig Venter. I think that is going to be discussed in extreme detail tomorrow, and I would hate to preempt that session so I will defer that question until tomorrow.

Question. I would like to ask Mr Gajdusek the following: In 10 or 15 years, when we have the entire human genome decoded and on the table, what kind of things will we able to learn about a person by analyzing or taking a look at this genome?

Carleton Gajdusek (Moderator). It depends on what you want to know. Obviously, if we look at those portions of the

genome that are involved with specific mutations in autosomal dominant disease, which is delayed in appearance in the life span, and which has high penetrants –which we can only determine by clinical experience in different places (because we have discovered that for a single gene here in Europe penetrants can be zero or high, depending on environment). So we must be careful even about experience in one part of the world predicting what it means in another. We now have perfect examples of autosomal dominant late disease causing fatal disease but not penetrating under one environment and penetrating under another. When it comes to predicting anything about personality or experience, I use domestic animals, horses, dogs, fighting cocks, as examples of personality breeding that has succeeded long before the genome project. I do not know whether we ever will be looking for ability types and disability types and the complex multigenic factors that will determine them, but I made a big point of the fact that the actual processing of data, the software for the human brain and mind is largely environmentally determined on top of its genetic basis. So with that in mind, identical twins, identical genomes can have a totally different behaviour and even brain structure, depending on childhood sensory input.

Answer. Just a quick additional answer to that question. The genes lead us to the proteins. We know only a very few proteins and their functions in the human cells. But the easiest route to discovering the proteins and how they direct the chemistry of the cells and direct development is to uncover the genes which give us the protein sequences.

Carleton Gajdusek. I wish to make one more point, when you think in terms of all the properties in the evolution of knowing the genome. Without knowing too much about it, the genome has been used extensively in agriculture to develop by cloning and in-breeding the types of species we want in animal husbandry and in agriculture. But it has also led to completely unpredictable results. No one on earth would dare predict what it means in terms of the more rapidly evolving microbes that affect those plants. And as a result, many of the genetically engineered plants have been wiped out by viroids and other recently evolved microbes, which we have no way of predicting or handling. Therefore, anyone who even dreams of manipulating a germ line as we have done in our agriculture and animal husbandry will produce an increase in susceptibility, and an increase in the evolutionary speed of pathogenic microbes which we have no ability to predict from reading the human genome.

Question. I will address this to whichever panel member would like to answer. There was a recent press report about the treatment of certain genetic diseases, monogenetic ones, with

mother cells extracted from the mother's umbilical cord. These cells with modified genes have even been applied in 5-day old infants. So my question is in reference to what is gene therapy. What level of precision do we currently have in placing the genes we need in the locations where we really need them? And what is the diagnostic value –this is an additional question– of the genetic tests that are now beginning to be administered? What value will they have in the future?

Answer. I will answer you in relation to a specific disease on which I worked during my stay in Paris, cystic fibrosis of the pancreas, which I discussed earlier and with respect to which I would now like to briefly review certain aspects. In 1985 chromosome 7 was located; in 1989 the gene was completely characterized, and at this time, as you already know, gene therapy has begun. The latest news reaching us at the international cystic fibrosis consortium, from just 20 days ago, is that the gene has 300 mutations in all. As for the question on gene therapy, I will answer on cystic fibrosis. As you know, much progress has been made. The greatest problem with cystic fibrosis –if you say precision– is that in this specific case we use an adenovirus whose pathogenic capacity has been eliminated. So the basic problem facing us, and which came up at the last North American Cystic Fibrosis Congress is that the pulmonary epithelium, at the first epidermic layer, is very problematic; there is constant scaling. Consequently, if this is what you were referring to in terms of the reliability and effectiveness of the treatment, I imagine that upcoming investigations will show that progress is being made step by step in that direction.

Question. I would also like to make reference to diseases caused by defects in more than one gene, that is, polygenetic diseases. In this respect the prospects seem to be fairly poor at the moment.

Answer. Well, in my modest opinion and understanding, I believe that progress in monogenic diseases is beginning, and the great problem confronting the people working in the field of multifactorial inheritance is precisely that the environment and, let's say, the genetic part both have an effect. Thus, I do not believe that great strides are being made –as my fellow panel members could discuss– in this field.

Question. I would like to ask Dr Grisolía for a summary. These 2 years of evolution, of the changes that have taken place, have they generated new fears with respect to the issues raised in Valencia? This distance of 2 years, going from 2,000 to 20,000: have they produced new fears? Are there new danger areas –if you will– developing, on the technological front or purely scien-

tific front, for that human dignity which forms the base of that whose preservation was sought?

Answer. I will answer from my point of view. You ask about the fears. Well, I do believe that the fears are, should be, the same now as the ones of a few years ago, but I always think –I do not know if it was made clear in my talk– in the responsibility of the people working in this area. Therefore, I do not believe there are new fears; the fears are the same. Perhaps, the more one discovers the more one's knowledge advances. It was mentioned in one of the talks; the deeper one delves, the frontier of mystery, let's say, will always continue to advance in science. So, in a way, I think the fears are unfounded as from the moment when common sense –which is the great advantage that human beings have, produced by reflection– rules in these research centres and laboratories. I don't know if Professor Grisolía would like to add his remarks.

Santiago Grisolía. No. I believe you are right, but, anyway, I think the questions should be more directed to you and, above all, to the spokespersons who are present here.

Charles R. Cantor. I think what has happened since the Valencia meeting has been a tremendous increase in the pace of discovery throughout the whole genome project. Technology is moving ahead. Progress made at the Genethon with mapping, our own and other progress with gene discovery has in fact shown how little information we actually had on which to base our knowledge of human physiology and biochemistry in the past. The tremendous burst of knowledge and information, without an understanding of that information, can lead to fear. So there may be increased fears, but that can be handled by having increased information, explaining to the public and press that there is a huge difference between genetic therapy of an individual and any attempt, at any stage, to touch the genomic constitution of the species. The ignorance is such that this would not be justified, from my own point of view, in this decade or the next decade, because of the huge variability of phenotypic expression we have learned to expect from every single gene in different environmental situations. And the enormous complexity of possible interactions of one gene and its product in the whole function of the species' adaptation is beyond our ability to predict or even to know how we will predict it. So we are not talking about the same thing when we speak of the gene and altering the gene in the individual as when someone suggests breeding humans the way we do our domestic animals and plants. We have been doing that kind of cloning and gene manipulation without really knowing what we were doing, and experiencing the difficulties of lack of predictability. The genome project will not give us that ability to

predict. Therefore, we must have our fears, I would say, linked very heavily with any suggestion of genome manipulation. But at the site of therapy, that is a different matter.

Question. I would like to know what is the magnitude, the difficulty in mapping jumping genes, and what level of information exists as to genetic horizontal transmission.

Answer. No evidence, not in the human anyway.

Question. There is no evidence of horizontal transmission, but could you clarify for me if there exist jumping genes in relation to the human genome?

Answer. The only evidence that I think could be construed as genetic horizontal transmission is the fact that in the infectious stage of Creutzfeldt-Jakob disease, which are infectious proteins of the host, an infected host like the cows of England produces from its protein, which is determined by its genes, a new infectious agent different from that which entered it. There genetic information has been horizontally transmitted as a pathogen. This is the only such example I know of in mammals.

Question. I would like to know what level of coordination exists between research efforts on both sides of the Atlantic, between research work in the United States and in Europe, as well as in Japan.

Answer. I would say there is tremendous cooperation and sharing of all physical materials and data. Now, instead of one genome meeting there are several dozen a year, all as international as is this meeting. So there is frequent discussion involving all interested parties in the genome; I would say there is tremendous cooperation.

With respect to cooperation on both sides of the Atlantic, of course, there exists a lot of collaboration, because scientists know each other and they have good reasons for collaborating. But we do something more. We have certain areas where we do systematically cooperate at the level of funding agencies, etc. And I would like to mention only two of them, and they are the efforts on the single-chromosome workshops and the efforts concerning the central database, the genome database.

I can add that in Japan there is already a society devoted to international bioethics seminars on the genome project. They held their second meeting in 1992 in Pukuwi.

Question. For me, just one more question, directly related to what Mr Klepsch said. Is there only cooperation on a European Community basis or is there also sponsoring of specific research done in Europe? The impression we have obtained today is that there is much more research on the other side of the Atlantic, and here we have documentation in bioethics but not so much research, except for our distinguished colleague from Spain, who I hope will excuse me, as he is the exception.

Answer. The research programmes we have developed exist on top of the research programmes going on in the Member States. We have and give direct support to research projects and to make the existing infrastructure in Europe available to all scientists. Over the last 2 years this support amounted to 50 million Ecu, and will continue for the next two and a half years on the level of 23 or 27.5 million Ecu. This goes directly to research projects on top of the activities which are going on anyway in Europe on a national basis.

Craig Venter. I think it would be an unfair characterization to imply that most of the research is going on on the other side of the Atlantic Ocean. There are tremendous breakthroughs which have occurred here in Europe. That there is transatlantic exchange is demonstrated by the YAC technology, which was developed by Maynard Olsen, expanded and used by Daniel Cohen, leading to the mapping which has now gone back across the Atlantic to be used in additional programmes there. I think there is tremendous research going on in the genome project in Europe. The first chromosome actually sequenced was the yeast chromosome, in an EC-supported project. So I think it is unfair to characterize it as one-sided.

Answer. I would just like to say that Dr Venter has answered what I wanted to say. In France at least, due to public charity it was possible to make great efforts in genetic mapping and in genetic physical mapping of the human genome. This was a tremendous effort made possible by public charity. Actually that is a very important point. Not all the money for supporting genome research in the world comes from governments. As a matter of fact, it is now estimated that half or less than half of the money supporting genome research comes from various governments.

Andreas Klepsch. I would like to add something which makes the comparison between the US and Europe even more difficult. I think I showed a transparency of all the projects we are doing in several sections of our research or activities, ranging from these to the human genome. But the human genome programme I was reporting on was exclusively dealing with the human genome. While as I understand it, in the United States something like

sequencing yeast would be regarded as part of the genome initiative.

Carleton Gajdusek. Do we have any other questions from the audience or the speakers? I think then that as moderators of this session we will call it to a close. I thank you all for your participation, the speakers, the audience and the people who have asked questions. Thank you.

MAN'S FREEDOM AND THE HUMAN GENOME

PRESENTATIONS

UTILITY OF YEAST ARTIFICIAL CHROMOSOMES (YACS) AND GENOME MAPPING FOR GENE THERAPY, AND SOME PRACTICAL CONSEQUENCES

David Schlessinger *

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YACs to find genes and provide them intact for gene therapy

Scientific results often interface with complex ethical and political issues, and thus with the codified expression in law of the moral views of the public. My comments are limited to a brief discussion of ways in which genome mapping in general and YACs in particular are contributing increasingly to the prospects for gene therapy. Fulfillment of those prospects could enhance man's freedom.

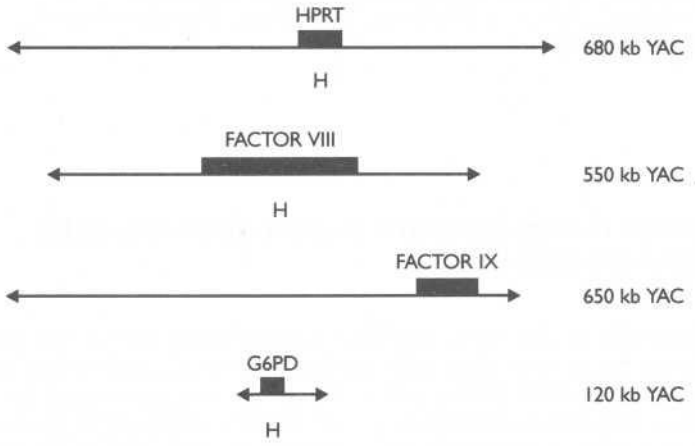
The power of YACs is a consequence of their large size compared to earlier cloning vectors like plasmids and cosmids. As a first indication of their potential, the large size of YACs permits the recovery of even large genes in intact form. For example, in the project to study the distal 50 Mb of the X chromosome that

* Moderator.

my laboratory has participated in, we early on recovered YACs for each of four genes important in inherited disease.

In the accompanying figure we see YACs illustrated which contain the genes for the two coagulation factors, Factor VIII and Factor IX, which are respectively defective in the A and B forms of hemophilia. The other two YACs shown contain HPRT, the gene defective in the Lesch-Nyhan syndrome, and glucose 6-phosphate dehydrogenase (G6PD), defects in which produce a form of hemolytic anemia. None of these genes had previously been recovered in intact form –in fact, work by a number of molecular biology groups over several years had assembled a series of much smaller lambda clones and cosmids, each about 15 to 40,000 base pairs (15 to 40 kb), that spanned the coding region for Factor IX (in the Figure, short lines below YACs indicate the content of typical clones of this type). In contrast, the YAC isolated with a Factor IX probe by Randy Little contained the gene intact in a continuous DNA segment of 650 kb.

FIGURE 1
Cloning in YACs or bacteria



As another example, Eric Green recovered an even larger gene intact. The gene, coding for the receptor modified in cystic fibrosis, was first isolated in an overlapping series of YACs. In this case, the initial YACs still carried only part of the gene; but by recombination, a larger YAC encompassing the entire gene was obtained. In an even more impressive reconstruction, Von Ommen and his colleagues did a series of crosses to assemble a single clone spanning the entire 2 million basepairs of the muscular dystrophy gene. Thus, no gene is too large to be carried in intact form in a YAC.

Such YACs offer the first possibility to supply gene therapists with a gene in intact form and in normal context. In the cases I have mentioned so far, however, there were already cDNAs and other pieces of the various genes available as probes. A more general and seminal use of YACs and genome mapping has been in the finding of genes that had not yet been cloned at all. The principle of such studies is clear: to localize a disease gene by linkage mapping or cytogenetic means –for example, a translocation or deletion in favorable patient material– and then to isolate DNA across the corresponding region and hunt for candidate genes. This is a traditional effort that motivates much human genetic work.

The relevance of YAC-based mapping and the Genome Project to such endeavors can be seen by contrasting two recent examples. Francis Collins, director of the National Center for Human Genome Research at the NIH, has estimated that in the hunt for the cystic fibrosis gene, a number of large laboratories and $100,000,000 were required to find the gene, and that 80% of the time and effort were required to get the DNA that covered the region indicated by genetic linkage studies. In contrast, in the recent successful search by the groups of Bruton and Bentley, using YACs to look for the basis of Bruton's agammaglobulinemia, about 80% of the time and energy required to find the gene again went into covering the region of interest with DNA, but the total cost was 100 times less.

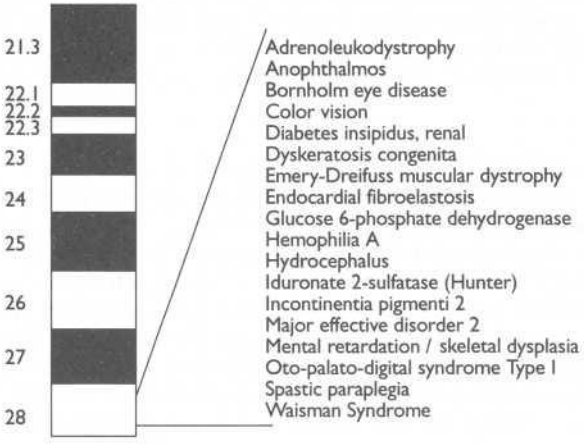
This capacity of YAC-based mapping to make disease gene searches more efficient will become stronger and stronger as more of the genome is assembled in DNA clones –and in fact, that is one of the principal goals of the genome project. When the entire genome is assembled in the coming years, instead of spending most of the time reisolating portions of the human genome, investigators who have localized a gene to a chromosomal region will be able to ask for DNA containing that entire region from a repository where the entire genome is stored.

The process is comparable to making a map of a country. When surveyors measure an area, they can fit those measurements into a total map once and forever, and there is no need for the same regions to be surveyed over and over again.

Studies of genome structure themselves have a further impact on gene hunts. For example, now that large portions of the genome are beginning to be available in the form of overlapping DNA clones, it has been found that genes are not uniformly distributed along chromosomes. It turns out that certain regions contain more than 10 times the average content of genes. One of the first cases to be analyzed in some detail is near one end of the

X chromosome, and many genes, including many in which lesions are responsible for genetic diseases, pile up there (see accompanying figure). Such regions are then choice sources of material for intensive study.

FIGURE 2
Region near the end of the X chromosome



Impact of genome studies on some public discourse

Gene therapy is now involved in the first phase of an inexorable march of events, with a typical headline reading that the «National Institutes of Health Recombinant DNA Advisory Committe approves six gene-transfer protocols». Until now, however, most efforts are still done with partial genes or small fragments of genes, and in most cases it remains difficult to maintain cells with a corrected gene for long periods of time.

The ability to obtain large regions in mapped form, and with genes intact and in normal context, is one of the preconditions for gene therapy, and could be facilitated by the use of YACs. A first step toward such a goal is the development of methods to introduce and select for the retention of YACs in mammalian cells. Transfection methods have now been successful in introducing YACs into cells and even into transgenic mice.

The systems are still very cumbersome, and suffer from the fact that only low levels of YACs are usually recovered from yeast and are difficult to maintain intact and difficult to introduce into

mammalian cells. Nevertheless, one can imagine routes to alleviate current difficulties.

There has been a distinct decrease in the opposition to gene therapy in the last 2 years. It seems to reflect greater public knowledge of what could be involved. For somatic cell therapy, the line of argument is now incontrovertible: if the gene is broken, why not fix it? From the standpoint of medical ethics, if we are dealing with a debilitating genetic illness, we are certainly ready to treat, and we should therefore be ready to cure.

Opposition has also decreased in part because the protocols are becoming less heroic. For example, in several instances bone marrow cells deficient in a particular gene can be sampled, receive a functional copy of the gene, and then placed back in a patient with restored function. Compared to current medical treatments in which all of the marrow in a patient is suppressed by irradiation and completely new marrow is imported from another person, somatic cell therapy seems less severe.

The enthusiasm that somatic cell therapy often engenders now is of course not matched in discussions of germ-line therapy; but I am among those who expect that once again, if procedures become safe and effective enough, opposition may decrease.

It may be worthwhile to distinguish the impact of current trends in relevant research on three types of fears of gene therapy that influence public policy.

First, there is the simple point that there remains a serious discrepancy between the information we can obtain from the diagnosis or genetic analysis of individuals –for example, in instances that are frequently discussed, sickle cell disease or Huntington's chorea– and our ability to treat the condition. For the present, the problem can, I submit, only be dealt with by respecting the preference of individuals to know or not to know about conditions that remain untreatable. But it is obvious that one's attitude toward such problems changes drastically if gene therapy indeed becomes safe and general.

In an analogous way, one can expect that such procedures could defuse permanently the controversy surrounding abortion, since germ-line therapy would justify early prenatal diagnosis and intervention to alleviate serious genetic defects by correcting them.

Second, there is the general public fear of genetic experimentation. Such fears are well grounded, most of us would say, based

on the history of the 20th century. However, the fear of the public that monsters will be created by genetic manipulation is not justified for the future by the dreadful history of eugenics in past decades. Caution is certainly required, but public attitudes are now preconditioned in a society in which everyone knows the Frankenstein story but very few have learned about genetics and its potential to alleviate human suffering. Once knowledge about genetics becomes more general, public fears should still be with us, but with the more positive result of regulating gene therapy judiciously.

Third, there is a curious phenomenon in intellectual and often scientific circles: a marked discomfort that many feel about the genetic differences among people. This is notable among those who have certain ideas about what is important or motivating in human existence. In particular, those who believe that particular environmental factors –like economics or the class struggle– are the critical features that determine the course of our lives tend to shy away or oppose the hegemony of genetic factors that may dominate our lives.

It is ironic that many who are very interested in the obvious power of environmental factors have not realized that modern genetics and gene therapy can provide very important ways to eliminate genetic differences that create unfair burdens for individuals. With such defects eliminated and everyone on a more level genetic playing field, one could then more easily concentrate on critical environmental factors.

The tendency to pretend that genetic factors can somehow be ignored or minimized can perhaps be tolerated for many marginal situations; but it can reach the absurd. On the positive side, genetic diversity is a major factor in the survival of a species; and on the negative side, in an example of a case in which diversity rather results in serious deficiency, Charles Scriver has noted that thalassemic patients are essentially universally in favor of gene therapy for their condition as soon as it is feasible. Their opinion is perhaps more relevant to discussions of gene therapy than is that of social theorists. Once again, at least for the severe cases where medical intervention is already common, opposition will almost certainly decline as procedures become safe.

Two inferences

A very positive feature of the Genome Program is that it is the first massive scientific program which, in my experience, is having extensive public discussions before events have run away with

situations. For the discussions here, it may be useful to emphasize two inferences that are relevant to legal aspects of the Human Genome Project. First, gene therapy is coming, and will have a very great impact on public and legal discussions of a number of related issues. Second, until gene therapy is safe, it seems desirable to have much or all genetic information about an individual remain the restricted possession of that individual. Thus, whether someone is tested for certain genes or not, and who knows the test results, should be determined by that person. Once again, as gene transfer becomes safer and more reliable, views about testing may correspondingly change.

MAN'S FREEDOM AND THE HUMAN GENOME

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On freedom

Freedom is a condition in which a person determines his life and his actions according to his own nature and ideas. Freedom is indispensable to Man's self-determination and self-fulfilment. Freedom is limited, conditioned or curtailed not only by external factors but also by the inner dispositions of man himself. Individual freedom is always relative and never absolute because nobody can satisfy all his wishes without entering into conflict with those of others. Even anarchism, the most extreme ideology of freedom, which refuses any constraint imposed by the State, accepts the necessity of self-limitation.

The establishment of the just balance between individual freedom and the collective interests of the community has preoccupied philosophers since times immemorial. Those of the Enlightenment, notably Jean-Jacques Rousseau, believed that there need be no contradiction between the freedom of individuals and the rules imposed by the State, the latter having resulted from the exercise of their inherent rights by free and equal citizens. According to his philosophy, the relationship between those who govern and

* Keynote Speaker.

those who are governed is based on mutual agreement («social contract»).

One of most forceful statements on the subject of freedom was made in 1859 by John Stuart Mill. In his famous treatise «On Liberty» he analysed the nature and limits of the power which can be legitimately exercised by society over the individual. He pointed out that the struggle between Liberty and Authority is the most conspicuous feature in the portions of history with which we are earliest familiar. Mill developed his argument first with respect to the liberty of thought and discussion. Even where the government is entirely at one with the people it has no right to exercise coercion against the expression of thoughts or against discussion. «If all mankind minus one, were of one opinion, and only one person were of the contrary opinion, mankind would no more be justified in silencing that one person, than he, if he had the power, would be in silencing mankind». Mill then discussed individuality as one of the elements of well-being. This is man's freedom to carry his opinions into practice, as long as it is at his own risk and peril and does not do harm to others. Individuality follows logically from freedom of opinion: different opinions result in different experiments of living. Genome scientists today confirm the importance of the concepts of individuality and diversity not only in the fields of law and politics but also in the field of genetics.

Freedom forms part of a wider body of fundamental principles referred to as Human Rights, which are the inalienable attributes of all human beings without distinction of sex, race, colour, nationality or religious and political convictions. They are based on the self-determination of every individual. The State is the guarantor of fundamental freedoms. The mechanism through which it exercises its rôle is called law. Within the legal system there is a hierarchy of norms. All norms aim at ensuring legal security and predictability of conduct, but not all norms are the expression of a higher morality. There are «traffic rules» of society (for example, putting the clock one hour forward on the last Sunday of March) which can be changed without disturbing the wellbeing of the nation. But there are certain rules which the State must respect because they embody the fundamental rights of Man. Man enjoys these rights «praeter legem», not «propter legem». He has a remedy against infringement of these rights not only before the highest court of his own land, but where necessary, before international tribunals.

All international human rights texts (such as the 1948 Universal Declaration of Human Rights, the 1966 International Covenants on Economic, Social and Cultural Rights and on Civil and Political Rights, the 1950 European Convention of Human Rights or the

1969 American Convention on Human Rights) set out the freedoms of Man: freedom of thought and conscience, freedom of movement, freedom of expression, freedom of association, free choice of employment, etc. Where it is considered necessary to regulate or restrict the exercise of certain freedoms in the interest of the protection of the rights and freedoms of others, or the community as a whole, the Human Rights instruments indicate with great precision the «limits of the limits» (in German «Schranken-schranken»), so as to prevent that they defeat the very purpose of human rights.

Human Rights texts use the terms «freedom» and «right». «Freedom» indicates a power to do, act, determine, decide, choose. «Right» denotes a thing one is entitled to, as in for example «right to life». The exercise of a freedom is always a conscious act. Rights on the other hand are to be guaranteed even to persons who are unable to express their will or to determine their own fate on the basis of full understanding (such as infants, mentally ill, foreigners who do not understand the language, etc.). Therefore, rights need a higher degree of protection. Human rights instruments are particularly critical of the tendency of States to limit the exercise of certain rights in emergency situations [e.g. Article 15 (2) of the European Human Rights Convention] and forbid outright the possibility for a person to renounce his rights. Human rights are non-negotiable.

Information, the companion of freedom

When we examine Man's freedom and the Human Genome, we must begin with a simple question: what do people know about the Human Genome? It would be exorbitant to ask a person's views about something he does not know. Information is the companion of freedom. Freedom of information occupies a very special place in the catalogue of human rights. Not only it is a right per se, but it is also a right which is indispensable to the exercise of other rights. Moreover, it is the only right codified in international human rights instruments applying explicitly «regardless of frontiers» (Article 19, International Covenant on Civil and Political Rights, article 10, European Human Rights Convention).

It is readily admitted that the success and efficiency of the Human Genome Project depends on circulation of information within the community of human genome scientists. We are told that the task is so huge, even allowing for all kinds of machines replacing humans, that it cannot be done unless legions of scientists, institutions and countries take part. The building up of such an international alliance is important in order to avoid that different re-

searchers and institutions do the same work. For this reason there must be worldwide exchange of information. It is one of the major objectives to which the Human Genome Organisation (HUGO) is committed [Article 3 (1) second indent of HUGO's articles of association].

But what about the wider public? Even for people who are intelligent and have a good education and general knowledge, the human genome is mostly terra incognita. It requires quite an effort on the part of laymen to understand it and on the part of scientists to explain it. The difficulty is compounded by the use of new terminology, as well as the novel use of existing words. For example, what the genome scientists call «cartography» is very different from the science and art of my 17th century ancestors who were map-makers. Similarly, when I asked some years ago for a French translation of the English word «sequencing», I was politely told that no such a word existed in the French language. If the very existence of a term is denied, this is almost tantamount to denying the existence of the thing itself. How can the average citizen/taxpayer be expected to claim and enjoy his freedom in relation to something largely unknown?

If one goes into a bookshop and is served by an intelligent person at the information desk, one may now find some very useful and readable books. I found two, one on genetics in general *Genetic Engineering for Almost Everybody* by William Bains (Penguin Books 1987) who dedicated it «For my father, who asked me to explain what I was doing». The other book, on the Human Genome Project is, *The Human Blueprint* by Robert Shapiro (St. Martin's Press New York 1991), a delightful 412 page description of the Project, its history and the people involved.

Closing the information gap

But these private information efforts aside, we expect that those who fund, administer and execute the Human Genome Project should make every effort to close the information gap between genome scientists and the general public. If any survey or poll was carried out within a random section of the population with the following two questions: (1) do you know what is the human genome? (2) have you ever heard of the Human Genome Project? the reply would be, as matters stand now, negative.

At the 2nd Workshop on the Human Genome Project held in Valencia 2.5 years ago, Norton Zinder reported on the goals of the United States part of the Project. After describing this 15-year

effort requiring $200 million a year (in 1988 dollars) for the construction of a high-resolution map of the Human Genome, he said that one of the program goals was «... 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» (Documenta, BBV, p. 100).

At the end of that Workshop, the participants adopted a «Valencia Declaration on Ethics and the Human Genome Project» in which they reaffirmed, inter alia, their support for «... efforts to educate the public, through all means including the press and the schools, about genome mapping and sequencing, genetic diseases and genetic services». The Human Genome Organisation (HUGO) mentions at the very end of a recent fact-sheet, under the heading: «Areas in which HUGO is hoping to expand its activities»: «... the spread of knowledge about the Human Genome Project through all levels of society». The same document indicates that it understands by «all levels of society» the scientific community, non-scientists in influential positions, the next generation of biological scientists and the general public.

These various statements emanating from the human genome scientists themselves are not yet entirely convincing. Mr Zinder spoke about the need to involve the public when it comes to coping with the consequences of the Project, but was silent on the more fundamental question whether and how the public had been informed and involved before the Project was actually established. The Valencia Declaration states the aim of «educating» the public, which places the public in a passive and receiving mode. The articles of association of HUGO suffer from a similar shortcoming: they state that one of HUGO's aims is to encourage debate: and provide information and advice on the implications of human genome projects, but not they do not address the question of how to involve the public in the decisions concerning the creation or funding of such projects.

HUGO does list the spread of knowledge in society as a hopeful objective. But its presentation of society as being composed of scientists, future scientists, influential non-scientists (presumably those who decide on budgets) and everybody else («the general public») is puzzling. We are used to categorisations of society as being composed of men and women, young and old, rich and poor and so forth, but not of genome scientists and non-genome scientists.

In conclusion, it is desirable that the Bilbao Workshop, which is dedicated to the legal aspects of the Human Genome Project, should pay serious heed to the public's right to know.

Discussion within the genome scientist community

Apart from the obvious need for this Workshop to take more fully into account the public's right to know, is there also any need to pursue the discussions, started at previous Workshops, between the human genome insiders on aspects other than scientific and technical? The answer is affirmative, for at least three reasons.

First, the progress of the Project must be regularly publicised with regard to its estimated duration. Just as the builders of medieval cathedrals knew that probably not they, but their sons or grandsons would see the work completed, so we are aware that the Project will eventually involve researchers, politicians, funders or beneficiaries who are still teenagers today.

Secondly, while the Project is following its course, steady as it goes, the world is dramatically changing. Since the Project began, on 1st October 1990, we have witnessed a Gulf War (1991), a Rio Earth Summit (1992) and a total transformation of East and Central Europe. What these events have in common is that they have sharpened our awareness of belonging to one human family and of sharing one planet, with all the consequences and responsibilities deriving therefrom.

Out of the confusion of the Gulf War at least one very clear message has emerged: those who wield power are accountable to the world community. At the Rio Earth Summit, political leaders have bowed before a force they recognise to be stronger than they, life in the biosphere. As for the collapse of communism in East and Central Europe, it is too early to analyse its fundamental causes or predict its long-term effects. But is is already clear that among the major factors which have led to this collapse was the aversion of the people to a political system based on suppression and distortion of truth (for example truth about the state of the ecology). All these events provide a new background to the work being carried out by genome scientists.

Towards a *Ius commune genomi humani*

As the conveners of the Bilbao workshop have rightly indicated, the law relating to the human genome is at most in its infancy, in many respects «embryonic» and in some respects non-existing. Cynical commentators have observed that here is a new goldfield for lawyers. Such comments are based on the assumption that when in a new field of human endeavour there is a legal deficit, this will mainly be remedied in the courtroom. I do not agree

with this view which ignores the fundamental meaning ot the Rule of Law, as I will explain later on.

The complex of legal rules and principles applying to the human genome –«human genome law»– are widely dispersed over many areas of law and jurisprudence: human rights, patent law, health law, family law, sports law, data protection, etc. There are tensions and contradictions between these various legal disciplines as well as between the laws of different countries. There is, above all, a disturbing absence of law on several important aspects of the human genome. This absence is not yet being addressed systematically, but rather piecemeal, each time when the need arises. The Baby M law-suit in New Jersey is a case in point.

Situations of «non-law» occur either because the matter at issue was never imagined by the legislator or treaty-maker, the classical example being artificial human procreation, or because of fundamental controversies, or a combination of both. In such situations, governments and parliaments often can do little else than setting up committees or commissioning experts, in the hope that by the time they receive the reports, a public consensus may have materialised. This uncertainty about the future policy and law singularly contrasts with the character of the Human Genome Project itself which moves forward like a military campaign.

One can also observe in some quarters a tendency to rely on «market morality» for the solution of these problems. This attitude has been strengthened by the downfall of communism. It consists in believing that since science, industry and commerce have a public responsibility and conscience, they should be able to judge what is good for the public benefit and to formulate and abide by voluntarily accepted codes of conduct.

During the 2nd Valencia Workshop, frequent references were made to the link between knowledge and power. The Human Genome Project is going to build an immense store of knowledge. Are we satisfied that this will produce sufficient information and wisdom not only on the Human Genome but also on the legal principles applicable to it? and who will be the custodian of the information?

Great censuses and inventories have been recorded in the past, such as the Domesday Book in Medieval England. The Human Genome Project is the 21st Century Domesday Book: the most complete inventory of Man. It is being carried out mainly with money from the public treasuries. Its utilisation should be for the benefit of Man. As has been stated over and over again, the Human Genome as such is not capable of appropriation and constitutes the common heritage of Mankind. One should therefore

seriously consider whether the results of the Project should not eventually be entrusted into the custody of an agency representing the interests of the whole of Mankind, such as the Secretary General of the United Nations, or perhaps a specialised agency within the United Nations.

The rule of law

An explicit reference in the mandate of the Human Genome Project to the Rule of Law is desirable. The Rule of Law, to which all nations actively involved in the Project suscribe, guarantees legal certainty and security. The Rule of Law means not only that the law must be democratically adopted, conform to Human Richts standards, be just, known, equal for all and capable of confirmation by an independent judiciary. It also means that there must be law and that there should be no legal vacuum. New human genome law is needed to prevent a legal vacuum in the human genome field.

Human genome law is all the more essential as, by definition, the Human Genome Project and its applications will affect Mankind in centuries to come. Our responsibility and stewardship towards future generations imposes on us the duty to steer our present actions in such a way as to avoid irreparable harm in the future.

Various experts at this meeting will examine specific legal disciplines which are relevant to the human genome. We will hear about patent law, about liability and tort, about human rights and so forth There should be ample opportunity for going into the details of these various disciplines. As for our methodology I wish to recommend to the Workshop one resembling that of the Human Genome Project itself. We should try to draw up the map of human genome law.

This procedure would consist of three phases. First, we might seek to inventorise law which is already being applied to human genome issues with greater or lesser success. Then we might wish to examine gaps and overlaps, i.e. blank spots on the legal map and clashes between two or more bodies of law. Our ultimate aim should be to develop a «ius commune genomi humani», a corpus of law which integrates the various disciplines into a coherent whole which is capable of applying to all countries at all times.

The conveners of this Workshop have suggested that even though the subject is new, not to say futuristic, it might be worthwhile to return to the sources of our legal culture, such as

Roman Law. I heartily concur. The more I see of new problems, the more I realise that if not the same legal problems, at least the same kind of legal problems have arisen in the past. Just as the rationale of the Human Genome Project is to avoid double work, so a visit to the traditional sources of law will help to avoid reinventing wisdom already existing.

The human genome is the common heritage of Mankind. This means that all national law must be subordinated to the peremptory rules and principles of international law, which are «ius cogens». It is desirable that States acknowledge this by becoming parties to the international treaties which have a direct or indirect bearing on the human genome. I am referring in particular to the international and European human rights treaties and to the Rio Convention on biological diversity. The largest actor in the Human Genome field, the United States of America, is unfortunately lagging way behind other countries as far as signature or ratification of these treaties is concerned. This casts a shadow over the leading nation in the human genome field.

Regardless, however, of whether or not a particular country is a party to any of the relevant treaties, the legal rules set out in them belong to the corpus of general principles of international law which are binding on all States and can be invoked before national and international tribunals.

With regard to the articulation of human genome law, the first step for the regulators and for the lawyers assisting them is to make sure that the definitions are clear. There has for example been some confusion about three terms used in connection with the Human Genome: «Initiative», «Program» (American spelling, not mine) and «Project». The term «Project» or «global Project» is now mostly used to indicate the sum total of the interrelated American and other countries' programmes. (France, Germany, United Kingdom, Italy, European Community, Japan, Russia.)

The law relating to the various national programmes is generally uncontroversial. The research grants made by the competent public or semi-public entities –in the United States for example the National Institutes of Health and the Department of Energy– and the contracts they have concluded with a number of scientific institutions are governed by the same kind of law that governs other public contracts. The relevant rules deal, inter alia, with calls for tenders, procedures by which contracts are awarded, how the results are reported, or expenses audited.

There is controversy, however, about a number of matters relating to the results of the research. The first is who is entitled to access to information generated under a programme financed out

of the national budget? Is it not the case that the general public should be informed not only about the existence of a programme but also about the results? And connected with this is a «macro» question: how about giving poor nations access to information held by the rich? A further controversy concerns intellectual property rights. Where the human genome is the heritage of all Mankind, does this not preclude attaching to it any intellectual proprietory or exclusivity rights?

I shall not go into the merits of these questions, which will be discussed by various speakers during the Workshop. But I must say that as a lawyer I am puzzled by the fact that they have not been sufficiently anticipated in the framework of the contracts concluded between the DoE, the NIH and their research partners which has given rise to controversy at the highest levels of leadership.

The global aspects of the project

The Human Genome Project is not identical with its United States component. It is a wide cooperation framework. The question has therefore arisen whether the overall development of the Project is simply the sum total of the reporting and auditing procedures in each country involved and within the European Community. Or is there a case for a mechanism common to all nations participating in the Project?

With regard to the coordination between the various national components, not much information is available. I have been given to understand that there is an informal coordination forum in which this takes place. There is no evidence on record of a formal structure.

However, the community of genome scientists, convinced of their highly important mission which should command the respect of the public have taken an original initiative by setting up in 1989 in Geneva, Switzerland, an association under Article 60ff of the Swiss Civil Code, the Human Genome Organisation (HUGO). HUGO has no formal decision-making powers, but carries moral weight. It is a consultative and coordinating arrangement not between the governments or institutions of the participating countries but between the people involved in the Project. HUGO describes itself as an «enabler» rather than a «provider». It does not fund research, judge the results of research or have any financial hold over it. HUGO creates networks and channels through which information, help and encouragement flow. It enhances the notions of mutual benefit and global cooperation.

Another characteristic of HUGO is that it is non-profit making. Its regional offices in Europe, the Americas and the Pacific enjoy charitable status.

In legal terms, HUGO is an international non-governmental organisations («NGO»), just like Amnesty International or the International Athletic Association. An interesting consequence of this is that HUGO, as an entity, is covered by the 1986 European Convention on the recognition of the legal personality of international non-governmental organisations (European Treaty Series no. 124) which entered into force on 1st January 1991 and to which the country of incorporation, Switzerland, as well as the country of seat of the European Office (HUGO Europe), the United Kingdom, are parties. Moreover, Russia, where HUGO Europe operates a satellite office, has already declared its intention to adhere to this Convention. The importance of the Convention is that it can help HUGO to overcome problems of red tape which arise almost inevitably for an organisation operating in different countries.

HUGO is a self-appointed organisation. It derives its legitimacy from the eminent position of the personalities who have created it and who assume in it their own responsibility. It operates a system of election of members, ensuring that only scientists of standing will be admitted to its ranks.

The question remains whether the existence of HUGO satisfies the need for independent public supervision and accountability at the international level. Apart from the structural framework of the Human Genome project which will be wound up or changed when the Project has been completed, in or about 2005, there is the substantive question of the purposes the Project was set up for and the uses likely to be made of its results. The origins of the project clearly lie in the fields of medicine, molecular biology and biochemistry, but its possible uses will fan out over a much wider range. Expectations have been raised about its benefits to mankind, but fears have also been expressed about possible abuses.

Bioethics

Considerations about positive and negative aspects of the development of the biomedical sciences are being drawn together under the heading of bioethics, a rapidly developing novel discipline. The legal aspects of bioethics are taking shape, at the national and international levels, in guidelines, laws, treaties and in the setting up of national ethics committees.

A pioneering rôle in this field is being played by the Council of Europe's Parliamentary Assembly and the intergovernmental Steering Committee on Bioethics (CDBI), which embraces some 30 States from Western and Eastern Europe and has observers from non-European OECD countries (Australia, Canada, Japan and the United States). The Council of Europe's work is expected to culminate shortly in the conclusion of a Bioethics Convention, in which all countries participating in the Human Genome Project can and should participate. From the point of view of human genome law, the draft Convention is a combination of *lex lata* and *de lege ferenda*. The group of States negotiating the text envisage that their domestic laws will give effect to the general and detailed rules set out therein.

The Human Genome Project and the emerging discipline of bioethics do not entirely cover the same ground, however. It is a matter for consideration by this Workshop whether eventually «human genome law» and bioethics law should be integrated. Bioethics is concerned with the applications of the biomedical sciences as a whole to human beings. For example, organ transplants are governed as such by the rules of bioethics, but they do not form part of the Human Genome Project which is a research undertaking. On the other hand, the Project has an impact on matters not immediately within the present definition of bioethics. It will result in the development of a tool, the human genetic map, which will prove useful not only to the activities covered by biomedicine, but also to other activities, such as archeology or migration controls.

Whatever the name of the new body of human genome and bioethics law, there already is a broad agreement about certain principles which should constitute this law: respect for the dignity of the human being in all its stages of development, prohibition of applications contrary to the fundamental values of Mankind, equitable access to the benefits of biomedical sciences, prohibition of treating the human body or parts thereof as a commercial commodity, respect for the autonomy of persons undergoing medical treatment which involves genetic testing and counseling and confidentiality of genetic data.

Certain newly formulated principles are still waiting to be incorporated in the human genome law. Two of these are closely related, ie the duty of States to respect and not to compromise biodiversity, as solemnly affirmed by the Convention on Biological Diversity signed in Rio de Janeiro on 22 May 1992 and the principle that Man's genetic heritage should not be manipulated or interfered with. There is a school of thinking which proposes that the latter principle should find its way into international and regional human rights treaties.

The human genome and biodiversity

The Rio Convention has brought home a very important question, namely whether we can go on treating as fundamentally different human genome research and research on the heredity of other living beings. The conclusions of what Mendel first observed in 1865 in his pea patch in Bohemia, and Thomas Hunt Morgan in 1910 in his fruit fly laboratory in New York, apply to plants, animals and Man.

In Nuremberg in 1947 at the trial of the Nazi doctors there was unanimous agreement that one should not use human beings for medical experiments, especially as one could use animals for that purpose. Four decades later, when the 1986 European Convention for the protection of vertrebrate animals used for experiments and other scientific purposes was concluded in Strasbourg, that principle was seriously questioned and the desirability was expressed of finding alternatives to animal experimentation. The debate has flared up with new vigour with regard to xeno-transplants, i.e. breeding animals with physical properties resembling Man which can be used as reservoirs of transplantable susbstances for human beings. I shall not elaborate on the latter subject, which is not included in the brief which the organisers of the Workshop have given me, but I would fail my duty if I did not note it for the agenda. It contains at least three major questions: the slippery slope (we can apply tomorrow to humans what we are appllying today to animals), the opposite argument according to which there is no reason why one should deny animals certain standards which are claimed for human beings and thirdly the indivisibility of the biosphere.

Freedom and the human genome

Affirming man's freedom in relation to the human genome seems at first an absurdity. One of the few factors concerning his identity in which the individual has absolutely no voice or choice are his genetic composition and the place and date he was born.

I have carefully scrutinised the document describing HUGO and I have found in it exactly one locus containing the word «free», where it states that «... information stored in the relevant databasis is freely available to the genome community» (para.3)

Apart from the curious notion of «genome community», to which all living organisms can be said to belong, the term «freely» probably means, «without undue restrictions». I am less sure whether it also means «free of charge».

Going back to Roman Law, as the Fundacion BBV has suggested, does not bring us much further as far as Man's Freedom is concerned. Freedom was not the top priority of the Roman Empire where a large part of the population was composed of slaves, who were not legal subjects but objects.

The aspiration to freedom and independence has been, of course, fundamental to *Homo sapiens* throughout evolution. It is tempered by the constraints imposed on human individuals by the fact that they live in socially organised communities. «Freedom» therefore relates both to individual behaviour and to the existence of groups of human beings.

The statement in Article 1 of the Universal Declaration of Human Rights, according to which «all human beings are born free and equal in dignity and rights» indicates that in spite of all the observable differences between human beings –boy or girl, large or small, light or dark skin, etc.– all are entitled to equal protection under the law. The Declaration adds a provision which is rather unusual in a human rights instrument, where it enjoins all human beings to «... act towards one another in a spirit of brotherhood». The passage is unusual because human rights instruments are generally concerned with the relationship between the State and the individual, and not with horizontal relationship between individuals.

Of all the human rights instruments mentioned in this paper, the Universal Declaration is the only one binding all nations participating in the Human Genome Project, including the United States. It seems therefore desirable to refer expressis verbis to the Declaration, as a source of standards to be upheld by what HUGO calls the «genome community». In fact, article 1 of the Valencia Declaration does refer to a part of the Universal Declaration where it acknowledges that genetic information should be used to enhance the dignity of the individual, but there is no reference, here or elsewhere, to individual freedom.

The Universal Declaration has extremely important consequences for the practice of genetic science. It means that scientists dealing with human beings in various stages of development and health, should approach each and everyone of them as if they were a brother or sister.

We cannot fail to note an important questio: If human beings are born free and equal, what does this mean in relation to unborn human beings? The Universal Declaration does not take an explicit stand on that question one way or another. It indicates that as from the earliest moment of the existence of the human person outside the mother's womb and in spite of its obvious state of dependence, it must be treated as free and equal. What is the

case before that moment is not made explicit. We note, however, that the Declaration uses the word «human being» and not the term «every person» which is employed in other parts of the Declaration. The Declaration does not exclude that the «human being» exists before birth. The American Convention on human rights, concluded in San José on 22 November 1969, has taken the matter a step further, first by stating in article 1 (2) that «person» means «human being» and secondly, in article 4 (1) that the right to life must be protected «from the moment of conception». A consequence, drawn in para. (5), is that capital punishment shall not be applied to pregnant women.

Freedom of, freedom from

When we examine the notion of freedom in the context of the human genome, we should draw a distinction between two kinds of freedom: «freedom of» and «freedom from». It was in 1941 that President Franklin Roosevelt outlined four essential human freedoms on which the future free world should be founded:

«The first is freedom of speech and expression The second is the freedom of every person to worship God in his own way. The third is freedom from want and the fourth is freedom from fear.»

These freedoms have since been amplified in many worldwide and regional human rights instruments: the Universal Declaration of Human Rights (1948), the European Convention of Human Rights and Fundamental Freedoms (1950) and the United Nations' 1966 Covenants on Civil and Political Rights and on Economic, Social and Political Rights.

While all these instruments were adopted long before the Human Genome Project, their provisions remain totally relevant to this new field. Probably the most important freedom is the freedom from want, which has been translated in the health field by Article 12 (1) of the Covenant on economic social and cultural rights as the right of everyone to the enjoyment of the highest attainable standard of physical and mental health as well as by Article 15 (1) (b) which proclaims the right of everyone to enjoy the benefits of scientific progress and its applications.

But of course, these rights to freedom from want have little meaning unless in the same human rights context conditions are created for stimulating the development of science. That objective is set out in Article 15 of the Covenant under which States undertake to respect the freedom indispensable for scientific research (para. 3) and recognise the benefits to be derived from

international contacts and co-operation in trhe scientific field (para. 4).

The reason why these provisions are little known and hardly ever invoked by the scientific community is that they are not self-executing. They contain standards of achievement and States are expected to submit reports on the observance of them, but there is no machinery through which States can be obliged to comply.

Much more forceful are the provisions of the civil and political rights instruments, such as the European Convention of 1950 and the UN Covenant of 1966, which are capable of control by international jurisdictions on behalf of individuals. For the interested persons, there are several important rights which they can invoke in connection with human genome research, such as the right to life (article 2 of the European Convention), to respect for private and family life (article 8), to marry and to found a family (article 12).

For the human genome scientists, the most fundamental freedom is that of scientifc research and investigation. We note that this freedom is not as such protected under the Human Rights Convention, but it is implicitly covered by the freedom of expression, which includes the freedom to hold opinions and to receive and impart information and ideas (article 10). This conclusion is supported by the famous provision of article 5 (3) of the Grundgesetz of Germany of 23 May 1949, which holds under the heading «Freedom of expression» that «Art and science, research and teaching are free.» This article has a venerable history, going back to the 19th Century when the King of Hanover dismissed on purely political grounds a group of professors at the University of Göttingen. The freedom of research and teaching was carried over into the Weimar Constitution, abolished by Hitler, but rapidly restored after the foundation of the Federal Republic.

Conclusion

It is desirable that the Governments funding the Human Genome Project and the partners in that project proclaim their commitment to the Rule of Law and to Human Rights. They might wish to stress in this connection that the aim of the Project is to further for the benefit of the citizens the realisation of freedom from want in the health field, and for the benefit of the genome scuientists the freedom of scientific investigation. All these freedoms carry with them obligations and responsibilities, which should be accepted in the spirit of brotherhood –and today we add sisterhood– advocated by article 1 of the Universal Declaration of Human Rights.

MAN'S FREEDOM AND THE GENOME

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A) From the standpoint of a philosopher of law, the Human Genome project, as described for non-specialists by Santiago Grisolía in an excellent article published in *Revista de Occidente* [1], represents one of those core problems which serve to explain and justify the existence of legal regulation in societies. In order take up this question it is necessary to first overcome certain prejudices and to understand a paradox.

Change, innovation and progress always stir prejudice. It may present itself with religious or metaphysical roots, or simply as superstition or fear of encountering what is unknown and unsettling. Sometimes the source of opposition is a sacred book, a theological or philosophical truth which cannot be doubted, or simply repression by a Tribunal such as the Inquisition. From some readings we may conclude present-day culture also harbours this conservative bias [2] and that, as Antonio Machado might have said, disdain is bred of ignorance: an infinite capacity for the destruction of human beings and human dignity is attributed to advances in genetic engineering. That is the mentality

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* Keynote Speaker.

[1] See *Revista de Occidente*, n.° 142, March 1993, page 19 and ff.

[2] See for instance the article by Bernard Edelman, «Génetique et Liberté», in the Magazine *Droits*, n.° 13, PVF, Paris 1991.

which Dewey called the revolt against science, which touches on the ancient conflict between science and religion, and the resultant «subversive theoretical effect exercised by new conclusions on established beliefs» [3]. Truly the use of what we could term genetic ideology in Nazi Germany and its terrible consequences makes such fears much more credible and explains the project's rejection by so-called alternative groups [4].

The paradox arises because the Human Genome Project, with everything it entails, is a consequence of scientific freedom, of the right to conduct research and engage in scientific and technical production which is part of the catalogue of fundamental rights. In other words, it is a consequence of a climate of radical freedom of thought which was one of the gains achieved in political culture with the transition to modernity. But such an origin is no guarantee that this scientific achievement of such importance for our present-day and future culture will not, in certain circumstances, become a danger to human beings and their rights, thereby generating the need for new protections and new rights. And that is the root of the paradox: that, instead of only producing benefits, the exercise of a right may produce hazards or evils which oblige us to defend ourselves. Many analyses of these problems in the Anglo-Saxon tradition also turn on this paradox, though identified with the «risk-benefit» dialectic that, according to Yvonne M. Cripps, is always involved in the «technology of genetic engineering» [5].

The following reflections are made attempting to avoid the carbide of prejudices against genetic research as well as the frivolity of believing that all the possibilities introduced by these scientific conquests may be realized without problems. Eschewing total pessimism and total optimism, they are grounded in realism.

B) The successful completion of the human genetic map, that is, of the complete series of instructions for the construction of a human being, and the possibility of discovering our own individual genetic identities, apart from their repercussions for genetic medicine, obliges us to reflect, without falling into either doom-mongering or naive optimism, upon their significance for the idea of human dignity and the great values such as freedom at the heart of our conception of modern political and legal culture.

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[3] John Dewey *Problems of Men*. Quote is translated from the Spanish edition *El Hombre y sus problemas*. Paidos. Buenos Aires, 3rd ed. 1967, p. 182.

[4] See the paper delivered by Hans Martín Sass, «A German Point of View» in *Human Genome Project: Ethics*. Fundación BBV. Bilbao 1991, pp. 61 and ff.

[5] See *Controlling Technology. Genetic Engineering and the Law*. Praeger. New York 1980.

These general considerations are necessary before taking up the subject of Law and the Human Genome Project.

We should begin by stipulating what is meant by that idea of human dignity, as well as by the different meanings of the word freedom.

1. Human dignity is the special consideration merited by humankind on the basis of the recognition therein of several traits which constitute the expression of that dignity and at which all modern discourses in the realm of legal, moral and political philosophy intersect. Human beings are capable of choosing between different options, of reasoning, and of constructing general concepts, of communicating with fellow humans, with whom they form a dialogical community, and of deciding upon life plans for achieving plenitude and moral autonomy. When we speak of human dignity, therefore, we are considering those features which distinguish humans from other animals as beings characterized by choices, reasons, dialogue and purposes. In any case, though it may appear obvious, we must remember that the idea of human dignity, like all the other ideas dealt with in the arena of moral, political and legal culture, is a construction of human thought, linked with the trait which shapes the very idea of dignity, our capacity to reason and to construct general conceptas [6].

2. As for freedom, referring to human freedom and its relation with the Human Genome Project by itself does not provide the necessary elements for comprehension, because the term freedom is univocal. We must posit at least three senses: freedom of choice, moral freedom and social, political and jural freedom.

Freedom of choice is an anthropological fact of the human condition, differentiating us from other animal and permitting us to choose when presented with various alternatives or distinct possibilities. It is the trait which led Max Scheler to say that man is the only animal that can say no. Also known as initial freedom or psychological freedom, it has been challenged by determinist outlooks, although human culture has made it one of the axes of its very existence, and of the existence of history and morality.

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[6] In this respect, the explicit recognition of the jural value of the idea of human dignity is found in Judgement 53 of April 11th 1985 which decided on an appeal for review as unconstitutional of the draft Act reforming article 417 bis of the Criminal Code (legal ground n.° 8) in connection with article 10 of the 1978 Constitution, and in assorted international texts from the United Nations Declaration of 1948 to the 1966 Covenants in application of the Declaration.

Rejecting human freedom of choice would undermine the great edifice of thought on humankind and on society.

Moral freedom or moral autonomy or independence, is the product, the goal, of the freedom which issues from psychological freedom and which consists of the free selection of life plans, of strategies for the pursuit of happiness, or, put in a more traditional way, the adoption of ideals of goodness or of virtue as the private morality of each individual. It is perhaps the utopia of the human condition. Moral freedom is the consequence of free will exercised in social, political and legal conditions favouring the normal exercise of our freedom of choice.

These two notions of freedom are inseparable. Freedom of choice without a goal, that is, which does not aim at the achievement of moral freedom, is choice for the sake of choice, devoid of meaning and leads to scepticism and radical ethical subjectivism. Moral freedom not based on free will implies something we are obliged to achieve because it is moral truth and as to which our opinion is insignificant. We may even have it imposed on us willingly, as seen in dogmatism and fundamentalism [7]. What I call the dynamics of freedom is that open communication which leads from freedom of choice to moral freedom. We may say that it is the path of morality and that is coincides with the traits which configure human dignity: the capacity to choose from among various options, capacity to reason and communicate, and the capacity to follow a path, a life plan for achieving plenitude. The autonomy-universality dialectic requires moreover that such a life plan be accepted by each subject (autonomy), while at the same time being susceptible of generalization, as an option which could become a general law (universalization). In these two notions we are not contemplating jural dimensions of freedom but, as we shall see, notions which are indispensable for a proper conception of law and for adopting a stance on Law and the Human Genome Project.

If we could isolate them in a laboratory, like biologists or physicists, that is, if they were possible without societal life, without relations with others, our thinking would change radically, and we could then perhaps dwell solely on the ethical aspects of the passage from initial freedom or free will to moral freedom. However, as Ortega would say, man is made of people living in society, where such phenomena as scarcity, limited altruism, and human selfishness are found, along with violence and power, to

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[7] For a more extensive treatment of these arguments see my book *Curso de derechos fundamentales*. «I. Teoría General. La libertad social, política y jurídica» [Social, political and jural freedom]. Eudema. Madrid 1992; pp. 184 to 207, particularly pp. 195 and ff.

name but some of the phenomena that most interfere with the dynamics of freedom. Hence man's need for law [8]. Legal-political social freedom is always freedom by means of the rule of law. It is the highest value or the principle constituting, together with equality, security and solidarity, the public ethics of modernity incorporated into social organization through a Constitution, law or judicial norms. Its ultimate sense, which in a democratic society is converted into the aim of public power and the law, is to make possible the attainment in society of moral freedom, through the possibility of the free, unfettered exercise of free will [9]. It is jurally constructed as a legal value or principle and developed through fundamental rights and principles of organization, and constitutes what we may call legalized public morality, which establishes as the law's central mission the objective of organizing society in such manner that each individual can freely choose his or her private ethics. It is an instrumental freedom, mediating between initial freedom and final freedom.

C) In a seminar dealing with legal aspects of the Human Genome Project, and specifically with «Man's Freedom and the Human Genome», the distinction we have just made between the three different meanings of freedom will be extremely useful. For though the legal aspects of the genome project and the law will take up the question of legal or jural freedom, we must ponder its repercussions on freedom of choice and moral liberty, as they effect the equilibrium of the entire edifice of humanity and human culture. In any case, it would seem that the importance of the subject and its implications for human dignity and freedom, as well as for countless other concrete aspects, warrants the intervention of positive law, and a legal-philosophical reflection on the moral dimensions which positive law should assume in order to assure freedom of research on the Human Genome without causing harm to the individual or to the collective. Such a reflection must be conducted from the standpoint of our culture's legal and ethical traditions, and not from biological positions or by the pundits of human genetics.

These are the traditions which should frame the legal channels, the constraints on the rights to be protected and the duties to be

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[8] In classic explanations such as Hume's *Treatise on Morals* or modern ones like Hart's on the concept of Law, it is these same problems which explain the existence of Law. See Hume's *De lo moral y otros ensayos* [On Morals and Other Essays], Centro de Estudios Constitucionales, Madrid 1982, edited by Dalmacio Negro Pavón, third section «De la justicia» [On justice]. See Hart *El Concepto de Derecho*. Published in Spanish by Genaro Carrió. Editora Nacional. Mexico 1990.

[9] See my address upon admission to the Spanish Royal Academy of Moral and Political Sciences «Etica Pública y Derecho» [Public Ethics and the Law]. Madrid, April 19th 1993.

performed. They must not do so, however, ignoring science but by bearing in mind its conquests, in this case the Human Genome Project. They are not corporatist rules for specialists. It is not a question of self-regulation but rather of applying general ethical, political and legal criteria to this field. When we speak of bioethics in regard to these issues, we are adopting, perhaps inevitably at first, the vista of specialists who are the first to become aware of the problem and its larger implications and ponder it having regard to the ethical issues that confront them. Yet, almost from the very beginning, scientific discoveries, in this case genetic discoveries, affect non-scientists, all people, and even humanity as a collective. Thus, more than of bioethics, we must speak of bio-law and bio-rights [10]. The process which led to the production of the atom bomb alerted us to the problems inherent in ceding such issues to the scientific community and certainly to the invisibility of power. That is why Yvonne M. Cripps has written «the lessons of the past help assure that in the future the control of new technologies is firmly situated in the competence of those most affected by them» [11]. This requires political action by the State through the law.

Positive law always trails developments, very rarely anticipating them. Thus, as we are still in the very initial stages –for notwithstanding its enormous progress the goals of genetic research have not yet been attained –we are in a *lege ferenda* stage, in which applicable legal norms have not yet been consolidated [12]. This is a good situation for the issue to be addressed from the standpoint of the philosophy of law, on the basis of a sufficiently informed awareness of the scientific problems and the points of positive law involved.

Along these lines, I base my reflection on the relation between freedom and the Human Genome project on certain postulates

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[10] See Sergio Moccia «¿Bioética or Biodirrito?» in *Rivisti Italiana di Diriti e Procedura Penal*, 1990; n.° 3 pp. 863 and ff.

[11] «Controlling Technology...», op cit, p. 12 [Translation to English of the author's translation to Spanish]. Furrow Johnson, Jost and Schwartz have written along the same lines. *Bioethics: Health Care, Law and Ethics*; West Publishing Co., Saint Paul, Minnesota 1991.

[12] See the national papers on legislation regarding these issues presented in the seminar organized by the Law School of the University of Coimbra, June 11th to 14th 1992, sponsored by the European Commission. Such legislation is almost nonexistent in Denmark, Germany, Great Britain, France, Greece, Italy, Japan, Norway, Portugal, Spain, South Africa and Sweden, though there are laws on specific topics in Spain and interesting bills in France, the eventual fate of which under the new centre-right government we do not know. Of interest is the work charged by the French Prime Minister to the Council of State on December 19th 1986, which can be found in «Science de la Vie. De l'Ethique au Droit». La Documentation Française. Notes et Etudes Documentaires. Paris 1988. On the specific subject of filiation, see Gilda Nicolau's *L'influence des progrès de le genetique sur le droit de la filiation*, Presses Universitaires de Bordeaux 1991.

which I accept as conclusions of other works and do not pretend to demonstrate herein.

1. A person, each person, is much more than his or her own individualized genetic project, though the latter is different from that of any other. That is why James S. Grisolía affirms that «... individual experiences and perspectives continue to have a decisive importance in the formation of personality, although within the constraints imposed by genetic inheritance...» [13].

2. Genetic determinism, a sign of the influence of a Darwinian mentality equating the person with his or her genes in a kind of biological predestination, is a false idea. It pertains to a *jus naturale* perspective which equates mankind with his nature. Regarding differentiated social and racial groups as carriers of undesirable traits, such an outlook has brought with it horrible eugenically-inclined political decisions leading to genocide [14].

3. Genetic issues cannot be approached from an exclusively individualist standpoint. One cannot speak of «a person's genetic inheritance» ignoring that genetic structure's connection to future generations and that germ-line therapy can involve transmittable mutations. Hence, there exists a unique genetic heritage for each individual and a collective genetic heritage pertaining to all mankind. In its regulation of these problems, positive law must take into account the tension between the two values of freedom and solidarity which connect the most personal structures of each individual with the collective genetic pool, which is a public good and intrinsically linked to the idea of the general interest.

4. Without ignoring the dangers, cited in point two above, of genetic determinism's underlying postulates, today, when the influence of capitalism is decisive, especially after the collapse of communist regimes in the former Soviet bloc, the genuine dangers arising from the ever greater knowledge furnished by science are found in the widening drive for privatization and in the contemplation of all problems from the standpoint of their profit potential. Thus, the law must give careful consideration to constraints which can prevent this knowledge from being used neglectfully of the general interest, only fo-

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[13] See his paper «Mankind in Search of Meaning» in the already cited *Human Genome Project: Ethics*, pp. 183 and ff.

[14] See Bartha María Knoppers' «L'integritá del patrimonio genetico: diritto sogetivo or dirrito dell'Umanità?», *Política del Diritto*, XXI, n.° 2, June 1990, pp. 341 and ff.

cused on private utilization and profit under a marketplace «ethics», putting the power of science in the service of strengthening economic power.

5. However, a government monopoly of research could use the power of science to expand political power, particularly where such research is conducted invisibly and not out in the open. The dissemination and public awareness of the Human Genome program, and of the knowledge achieved by the new genetics generally, could counteract this tendency of all power to avoid being limited. Educational work on these problems and their ethical, political and legal dimensions would avoid the survival of false myths, prejudices, fears, insecurity, and also avert efforts by scientific powers, standing alone or supported by political or economic powers, to benefit from these gains in knowledge to the detriment of the larger citizenry's rights, that is, of freedom.

D) Free will and moral freedom are affected by the advances of the Human Genome Project. They require the action of law, based on jural freedom, to rationally organize communication, fix the limits, and determine the areas in which these discoveries may be used, by whom and with what requisites and conditions. And jural freedom, which as we indicated earlier is organized through in law into fundamental rights and principles of organization, is itself affected by the Human Genome Project and its implications for such fundamental rights as the right to physical and moral integrity, to personal and family privacy, to scientific production, the right to information, to an education, etc.

Thus when the subject of «man's freedom and the human genome» is raised, we see freedom as jural freedom, but at two different levels: first, indirectly through the prism of morality, of the dialectic between free will and moral freedom; second, directly through the prim of legality, although here too the essential issue is the protection of morality, of the freedom to choose life plans. Starting with the recognition and identification of its potential risks, so that we may better avert them, we study the Human Genome Project from the standpoint of morality –or legality– and of social, political and jural freedom. In the first case the project touches on human dignity directly, and, in the second, on the rules of law which protect it.

1. Pondering the Human Genome Project's implications for free will or freedom of choice calls to mind two problems: guaranteeing free will versus genetic-based determinism, and limiting the freedom to choose in some scientific avenues made possible by genetic advances.

Genetic manipulations which make it possible to orient human behaviour are a transgression of free will and should be prohibited, because they intervene at the starting point of morality, converting human beings into things. Here, the need for law seems quite clear here, as does the inadequacy of an exclusively ethical approach. The interests of third parties are affected, as is the general interest, seen as a specific outgrowth of mankind's free will.

To be specific, in our constitutional system this legal protection is achieved through article 15 of the Spanish Constitution, which protects the right to moral integrity and prohibits inhuman or degrading treatment. Take a hypothetical, and hitherto academic, case where a scientific project alters free will. Faced with the negative reaction such an effort would generate –from the scientific community, political power, pressure groups, or of whatever origin– the Supreme Court (filling in for the ordinary courts which would be first called upon to hear the issue) would find it easy to construct a legal argument justifying the prohibition of research, testing or experimentation with human beings possibly involving further limitations on intellectual, labour or social constraints.

This line of argument would find additional support in the whole of article 10.1 of the Constitution, particularly in its references to the free development of man's personality and human dignity as essential to political order and social peace.

Continuing with the hypothetical case, we could also come across a person who willingly volunteers to participate in such experiments aimed at discovering the extent to which free will is conditioned. The law would have to address such a case at several different levels.

a) First, we must consider whether the law should allow the free disposal by the subject of his free will and accept that he voluntarily submit to scientific experiments which could completely or partly determine his behaviour. In this case, the answer will depend on the position adopted with respect to the right to life. If the right to life is believed to include the possibility of disposing of one's own life –legal suicide– it would be consistent to uphold that the person may dispose of component aspects of his personality, such as moral integrity, which is life's expression and consequence. The partial suicide implicit in voluntary submission to the loss of some or all of one's free will would thus be acceptable. If, on the contrary, the right to life is not held to permit disposing of one's own life, but only of protecting and assuring it, a

protectionist position would be adopted and clinical experiments of this kind would be prohibited. I consider the second response to be more reasonable.

b) We must secondly address the situation of those persons who are not capable of giving free consent, and even less so if mediated by a price, because they are prisoners, of poor families, live in impoverished countries, are subjected to some sort of military or political discipline, etc. The law must be vigorous in its prohibition of uninformed consent.

c) Thirdly, the problem transcends individual cases and touches future generations when the manipulation consented to does not only affects the experimental subject who gave that consent but is also transmitted to the his or her descendants. In this case the principle of solidarity and arguments based on the impossibility of accepting determinants to which consent has not been freely given should compel the enactment of laws to prohibit consent which brings on such consequences. This case represents a qualitative leap, because we are no longer faced with a possible excessive use of a personal right, but rather a decision affecting the entire collective, humankind's genetic heritage.

In these three cases in which we have confronted the genome project with free will, the problems raised all point to the indispensable need for the citizenry as a whole to be adequately informed. Here, the Human Genome Project's far-reaching implications bring into play certain old demons, erstwhile foes of the rule of law: the ideas of national defence and public security as sometimes wielded to justify lack of transparency and the absence of adequate disclosure. Certainly, detailed information can favour industrial espionage and private corporations working in this field are not bound by the duty to inform, or at least not to the extent expected of public authorities. We may nevertheless put forward the idea that in the face of these scientific advances a guaranteed right to reliable information is one of the first legally protected requirements of morality and legality. Here the provisions of article 20-1d of the Spanish Constitution enter into consideration.

2. Entering now into the genome project's possible collision with moral freedom, the hypothesis to weigh is whether on the basis of the knowledge attained by this research a single moral conception can be presented as the only truth or

whether human beings can be divested of the essential condition of their dignity: their moral capacity, quest for autonomy, or moral independence. If it is possible that Huxley's «Brave New World», titled «Un Mundo Feliz» [Happy World] in the Spanish version [15], could produce beings morally guided by a truth imposed on them, research leading to such ends should be prohibited because it fractures the dynamics of morality, that hallmark of human dignity. If such a development were actually to come about this would be a different world, mankind would be different, and humanity as an enterprise culturally constructed throughout the course of history would be ruptured. Here too the search for support in the legal imperatives of jural freedom may be grounded in article 10-1 of the Constitution and its conception of dignity and the free development of personality, as foundations of public order and social peace, and in article 15's reference to moral integrity. Attention must be called in this case and that of manipulations of free will to the impossibility of complying with the constitutional mandate on the aims of education, which article 27-2 lays down as consisting of «...the full development of human personality...».

A study of the Universal Declaration of Human Rights and the international treaties and agreements thereon ratified by Spain, which pursuant to article 10-2 of the Spanish Constitution are to serve as guideline when interpreting rights, will clearly show that these texts are likewise fundamentally grounded in human dignity and in a dynamic of freedom which allows human beings their integral development as persons. Thus the Preamble and articles 1, 6, 12, 8, and 26.1 of the United Nations Declaration, articles 8 and 9-1 of the European Convention, and article 2 of the first protocol, to cite some examples which could be readily multiplied, underscore these texts' philosophical concurrence with the idea of human dignity and morality as has been described herein [16].

When, in summary, the dynamics of liberty are jeopardized, when the morality which is one of the most eminent and meaningful expressions of human dignity is endangered, the law must be set into action. The law must prohibit research which impacts on the starting point –that is, orienting or manipulating free will– as well as that which acts on the endpoint –that is, partly or totally

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[15] Huxley took the title of his book from a passage in Shakespeare's «The Tempest»; when Mirando, who had never seen any human beings other than his father and Fernando, sees the band of men brought to the island by the storm and exclaims «O, wonder! How goodly creatures are there here! How Beauteous mankind is! *O brave new world*, that has such people in it...!».

[16] See these texts in *Derecho positivo de los seres humanos*, edited by Peces-Barba, Hierro, Iñiguez de Onzoño, and Llamas. Debate. Madrid 1987.

replacing moral independence or freedom with the scientists' own morality or, more to the point, with the morality of the economic or political power behind such research.

E) We have seen the way in which certain lines of genetic research can affect freedom of choice and moral freedom, and how law must act to prevent such evils, laying down the limits of the benefits scientific enterprise can provide. In reaching these conclusions of a legal-philosophical nature, one of my criteria of reference has been public ethics as conceived in the modern age, based on the idea of human dignity and its jural codification into fundamental rights and principles of organization. It is now time to apply these general criteria to the organization of social life based on the concept of jural freedom. Certainly other legal sciences such as administrative, civil, criminal or labour law have bearing on the issues raised by the Human Genome project, but they should always maintain this perspective as a core reference. The reasoning of the French Conseil d'Etat is premised on the insufficiency of ethical reflection: «...ethics, which remains obviously necessary is not sufficient. Legal norms and institutions are indispensable for deducing the new procedures' consequences with respect to filiation or for avoiding derivations such as genetic manipulations...» [17]. In the opinion of the members of the nucleus of the French Conseil d'Etat, a minimum public order is to be established in agreement with what I have herein called public ethics, related to the «jural idea of man at the end of 20th century». They would have it based on the following principles: the indivisibility of body and spirit, inviolability of the body without the consent of the person, inalienability of the body, which is not subject to commerce [18].

Within the framework of this deliberation, which cannot be exhaustive, the following reflections at least strike me to be necessary.

1. A reflection on the manner of incorporating these issues into positive law

In my opinion it would be appropriate to consider a law specifically regulating all aspects of science and research which could jeopardize jural freedom and its materialization in fundamental rights and principles of organization. In Spain the right to physical and moral integrity as guaranteed in article 15 of the Constitu-

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[17] See «De l'Ethique au Droit»; see note 12.

[18] Ibid. pp. 15 to 18. They will centre the study with these principles on three aspects: scientific intervention on human beings; human procreation, assisted procreation, prenatal diagnostics, and the use of human embryos; and the legal framework.

tional provides grounds for protecting all dimensions of such rights with measures suited to the field, with particular regard to advances in genetic research though not prompted solely by these developments (other kindred problems such as clinical testing and transplants could be incorporated as well). It seems more positive to adopt this approach than to take up these issues as constraints on the freedom to research laid down in article 20-1b, formulated as the right to scientific production.

As the issue is one of regulating a constitutional (and hence fundamental) right, such regulation must be brought about by means of an Act of Parliament and moreover, as the right involved is a fundamental right within the meaning of article 81-1 of the Constitution, by an Organic Law, although the Act itself could set out which sections thereof are classified as ordinary for purposes of their amendment by such procedure.

A general legal framework is needed in order to avoid all issues being raised as specific instances of case-law, for the latter requires the passage of much time before it can achieve an integral overview and pivots on the interpretation of laws, with the attendant risks of legal uncertainty. Obviously, specific cases would still have to be decided upon and there will be many difficult issues to unravel, but there would be a general law that could serve as a central reference [19].

Although other fundamental rights such as the right to personal and family privacy, ideological freedom, and freedom of research may be involved, it seems appropriate to ground discussion of these issues in the right to physical and moral integrity, taken to comprehend the right to the integrity of one's genetic inheritance, with any modification thereof requiring justification. This preference for Organic Laws naturally entails accepting a normative hierarchy in these matters, which must of course be completed by administrative norms regulating the functioning of public bodies, such as the Health Advisory Board or a possible National Committee on Ethics, and by the judgements and legal doctrine produced by judges, what is known as case-law or bench legislation.

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[19] In the introduction to the French Conseil d'Etat's «De l'Ethique au Droit» referred to earlier, legislation is preferred over «...other procedures for elaborating law, custom, usage, such as that which applies in centres for the study and conservation of sperm, or case law...» (p. 14). It is an authoritative position and in agreement with what I advocate herein. Cristian Byk, in his paper «Lessons from the Past: Projects for the Future. The Human Genome Project and Social Contract: An Approach of Legal Policy» published in *Human Genome Project: Ethics* argues along the same lines when he write «...the courts are ill-suited to resolve all the questions in the context of existing law and the control of experimentation can not be accomplished by courts without any specific legal reference...» (p. 381).

2. *Different aspects of the protection of fundamental rights*

The law should first dictate that there must be no contradictions between this central right to physical and moral integrity, understood as the integrity of the each individual person's genetic inheritance, and the preservation of humanity's collective genetic heritage or pool. This is the integration of the principles of freedom and solidarity.

With such a declaration as a starting point, attention should then be focused on the most important aspects to be pursued by the law in protecting this individual right to one's own genetic inheritance [20].

- The right that no gene alteration be performed without authorization by the person concerned or his or her legally mandated representative if the person is incapacitated. This right could be restricted by authority of the courts where gene therapy treatment of a disease might avoid its transmission to the person's offspring.

- The right to sufficient information about the reasons for and consequence of a genetic intervention, and as to the possibility of its effects being passed on to the person's descendants. This right shall take the form of a formal protocol stating the information which must be known, signed by the informing scientist and, of course, by the person concerned.

- Respect for privacy and confidentiality so that none of an individual's genetic data be disclosed to third parties without the person's consent. Restrictions on this right will come into play when knowledge of such data is essential to the health or to

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[20] In Spain thus far legal doctrine has produced very few contributions on this subject and I think none of central importance from the standpoint of the philosophy of law. Among these we may cite Enrique Ruiz Vadillos «La investigación científica y el Derecho. Especial consideración de la ingeniería genética» [Scientific research and the law. Special consideration of genetic engineering] in *Revista General de Derecho,* 1986, n.° 504, pp. 3645 and ff; Gonzalo Higuera's «Repercusiones legales de la biotecnología en la reproducción humana» [Legal repercussions of biotechnology for human reproduction] in *Revista de la Facultad de Derecho y Ciencias Económicas*; ICADE, Madrid 1968, pp. 41 and ff; Albin Eser's «Genética humana desde la perspectiva del Derecho Alemán» [Human genetics from the perspective of German law] in *Anuario de Derecho Penal y Ciencias Penales*, 1985, n.° 38, volume II, pp. 347 and ff; Antonio Cuerda Riezu's «Limites juridico-penales de las nuevas técnicas genéticas» [Criminal-law limits on the new genetic techniques] and «Otra vez sobre nuevas técnicas genéticas y Derecho Penal» [New genetic techniques and criminal law revisited] in *Anuario de Derecho Penal y Ciencias Penales*, 1989, vol. II, pp. 413 and ff, and vol. III pp. 703 and ff.

the respect for the moral or physical integrity of another person.

- Each person's right to access their individual genetic data upon request, where such data is on record at an authorized registry or database.

- All actions in this area shall be free of charge to the interested party.

In addition to the foregoing rights which issue from the central right to physical and moral integrity, the law should contain prohibitions on public or private genetic research practices which are contrary to that right, that is, to the integrity of individual genetic inheritance and, at times, of humanity's genetic pool. These would include prohibitions on:

- Military or repressive uses of genetic information and on any state plan or programme designed to affect the genetic integrity of individuals and their progeny, or, where such is possible, to alter elements of humanity's collective genetic map.

- Genetic manipulation of incapacitated, physically or psychologically handicapped people, or other persons having diminished capacity to exercise their freedom of choice in such regard (detainees, prisoners, the poor, the ill or pregnant women).

- Genetic research leading to genetic manipulations devoid of scientific interest (extrauterine development of the embryo and fetus, or reproduction from a single unfertilized female gamete, that is, based on a single genetic heritage, or reproduction of identical organisms by distinct means).

- Eugenics based on the sex of the fetus.

- Genetic research interfering with a person's free will and moral freedom.

3. *Application of the principles of the organization of power and law to further the effectiveness of jural freedom and an efficacious protection of the right to physical and moral integrity*

This section will suggest those spheres of the organization of power and of law which insofar as concerns the Human Genome Project should contain certain principles of organization aimed at guaranteeing the jural freedom of the citizenry. Here we can point to the following as measures which should be taken:

- A government watchdog body should be appointed to oversee the functioning of the public services with responsibilities in this area.

- A National Committee on Ethics should be appointed, or the Health Advisory Board should be charged with the function of drawing attention to those emergent ethical problems not yet clearly addressed by the Organic Law herein proposed or by ordinary court case-law or Constitutional Court jurisprudence. This task of mediating in the definition of difficult new issues could serve to guide scientists, avoid conflicts, help provide courts with criteria for their judgements, and also suggest new areas in need of legal regulation.

- A procedure should be established for issuing an official catalogue listing institutions and bodies authorized to conduct genetic research and setting out the requisite conditions for being granted such authorization.

- Secrecy should be prohibited and transparency assured in government bodies and in the supervised private organizations. This entails a generic transparency principle, limited by rights to privacy, assuring that research findings are universally available.

- The secondary liability of competent government bodies should be set down as a principle for cases where the entity with primary liability for violating these rights, or for infringing the prohibitions set down in this field, is insolvent. In the case of an entity acting without the necessary authorization, government liability would arise for *culpa in vigilando* (negligent enforcement).

4. Sanctions

None of the provisions of the proposed Organic Law we have referred to make sense nor can their effectiveness be guaranteed without setting out sanctions for the violations defined thereunder.

- There non-criminal infractions occur there exists the possibility of proceeding against the researcher or promoter on the basis of their civil liability.

- Disciplinary sanctions may arise when the persons liable for the infractions are under some corporate discipline, e.g. as members of a professional association or public employees subject to a civil service statute. This requires that the corporations involved, and the civil service statue, address the effects on their

respective professions of the rights and prohibitions set out under our proposed Organic Law.

– Penal sanctions should be of two sorts. The first should punish actions taken in areas prohibited by law. As we have already indicated, acceptance by the affected person in no way diminishes the possibility of bringing criminal charges. The second kind includes cases where the research itself is legal but that certain legal provisions are violated, for instance, as to informed consent, cost-free status, therapeutic intention, etc.

Enrique Ruiz Vadillo, President of the Criminal Chamber of the Spanish Supreme Court, has proposed the incorporation into the new Code of a single criminal category integrating both types of sanctions. On the basis of that proposal [21], the following generic category, addressing the issue of penal guarantee, can be formulated:

«Those who with aims other than the elimination or diminishment of serious illness manipulate genes so as to alter the vital constitutional type, thereby violating the individual's right to physical or moral integrity, shall be punished with imprisonment of from 6 months and a day to 6 years and disqualification from engaging in such experimentation.

«Those who do so in violation of the applicable legal provisions or with gross negligence, in circumstances other than those provided for in the foregoing paragraph, shall be punished with the sentences immediately preceding the above in severity».

F) This initial discussion of the Human Genome Project and its legal aspects is, logically enough, rooted in the central moral values assumed by law and promoted by a political power which has previously incorporated them into its objectives and purposes. That is why the approach of law to such a discussion has fundamental regard to freedom, with all the nuances we have indicated earlier. Furthermore, it appears reasonable for the law to deal with these issues by means of an Organic Law implementing and applying the right to physical and moral integrity, in its connection to the idea of genetic heritage. This law would lay down general criteria and limit the freedom of what has become the scientific power establishment. Lacordaire always stressed that «between the strong and the weak, the rich and the poor, it is freedom which oppresses and the law which liberates...» [22].

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[21] See Ruiz Vadillo, «La investigación científica y el Derecho...», op cit, p. 3664.

[22] Included on p. 14 of the already cited «De 'Ethique au Droit...», see footnote 12.

Leaving this terrain orphaned of legal regulation could have incalculable consequences. Just as we rationalize political power with law, we must do the same with ideological, economic and scientific power. This reflection is one small contribution toward that end, although one made knowing that there are spheres which will be left to bioethics and that all regulation must be built with frontiers flexible enough to accommodate the evolution of scientific knowledge and progress.

In any case, the scarce jural codification of these issues is not only due to the doubts harboured by lawmakers, but also to the pressures exerted by those wishing to maintain a hegemony which reinforces ideological, economic or political hegemonies. Law, after all, cannot limit itself to specific interventions in the areas of commercial, labour, or industrial property rights, to name but a few examples. It also needs this radical approach rooted in the very essences of the legal system, the material criteria for defining statutes, values, rights and principles of organization.

PAPERS

TEN COMMON ERRORS CONCERNING ETHICS

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1. Making good use, perhaps abuse, of the freedom referred to in the title of this section («Man's freedom and the human genome»), this paper roams beyond the framework suggested by the organizers. Actually, the question I will try to raise here is preliminary to this and other sections and one which I think can at the same time serve to link the 1990 workshop, which took up an analysis of the Human Genome Project's ethical implications, and this gathering, in which the legal implications are to be discussed. The fact that my specialty is the Philosophy of Law, that is, a discipline that to some extent tends a bridge between philosophy –including ethics– and law is a good excuse for so acting. So good, in fact, that well pondered it could even serve as a justification. For if the aim of this gathering is to construe in the legal realm questions of ethics (that is, a matter of how to use the techniques of law to preserve ethical values that human genome research could harm or endanger), it is doubtless wise to first review the extent to which the underlying ethical ideas are valid.

   For professional reasons, I have a certain amount of experience in dealing with jurists on ethical issues. Now that my reading of diverse texts has given me the opportunity to know what scientists –or some scientists– think about ethics,

I have come to the somewhat surprised realization that both groups tend to commit the same errors when pondering these issues. Naturally, I do not pretend to say that jurists and scientists –geneticists– as a whole are astray with respect to ethics, but only that many, or some, of them seem to commit what in my opinion (or I should say the opinion of a typical philosopher of ethics) are conceptual and argumentative errors which do not exactly help foster a rigorous and fruitful discussion of the issues.

2. Ahead I will indicate some of these errors and enumerate (always wise in discussions of ethics) a total of ten. I will give some examples taken from the proceedings of the Human Genome Project: Ethics workshop and add some other brief remarks on the subject.

   2.1. The first error consists of confusing (or not distinguishing) ethics with the prevailing customs of a given society. When it is said, for example, that «ethics as such is not an objective discipline. Rather it tends more to employ principles that vary with time and people» and that «ethics represents and reflects the customs accepted by a society» [1], or that «science is universal» whereas «ethics and public policy are very provincial» [2], I am afraid that two things which should be separated are being confused. It is as if someone were to say that science (genetics, for example) is not universal because people have and have historically had different ideas about evolution (including the idea that we were created in the likeness of God). The analytical philosophy of ethics has long posited the distinction between descriptive ethics and prescriptive ethics. The former, that is, the description of a people's moral opinions, is not handled by philosophers but by social scientists such as sociologists and anthropologists.

   2.2. A second error is what may be termed moral subjectivism. It arises, as in the above case, when ethics, instead of being identified with a people, with what a people as a whole or a majority thereof think or practice, is considered as nothing but a collection of subjective opinions. These are not subjective merely because they stem from each individual as an ethical

[1] The proceedings of the II Workshop on International Cooperation for the Human Genome Project are collected in the book *Human Genome Project: Ethics*, published by the Fundación BBV, Bilbao, 1992. These particular quotes are from p. 14.
[2] Ibid p. 393.

subject (something which is inevitably true) but because they cannot aim to be valid beyond the scope delimited by the activity of that subject. For those who think along these lines, ethics is indeed merely a question of preferences. They thus emphasize that one must not seek to impose «my own preferences on others or to have others prescribe what is "right" for me» [3]. Or they hold that philosophy (in which ethics should be included) «studies mankind's subjective relation to the universe of natural things» [4], which can eventually lead them to contrapose «the objective (natural sciences) and the subjective (philosophy and religion)» [5]. Thus viewed it is obvious, and consistent, that ethics has no role to play with respect to the regulation of inter-subject conduct, the role aspired to by law. This radical ethical nihilism was expressed by one of the politicians who closed the 1990 meeting, whom we must certainly thank for his candour, when he stated: «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» [6].

2.3. One of the consequences of the two foregoing errors is a third error, consisting in identifying, or in not distinguishing between, law and morals. If ethics is by nature purely relative and subjective, and societal life needs fixed criteria of objective validity (inter-subjective), then it is not strange –as we have just seen– for law to end up replacing, and being confused with morals. The question as to what is right or good eventually becomes a question of what a given system of positive law considers as such. The preceding and following paragraphs contain several examples of this conception of law (and of morals), which is usually termed ideological positivism.

2.4. The replacement of ethical discourse by a pragmatic or instrumental discourse (that is, to consider ethics not as a question of aims but as one of means and instruments for achieving aims already given) represents the fourth of this catalogue of errors. This is the error committed by those, for example, who believe that implementing scientific or technical advances, given the

[3] Ibid p. 81.
[4] Ibid p. 189.
[5] Ibid p. 198.
[6] Ibid p. 430.

existence of limited resources, involves decisions which favour certain persons at the expense of others, and that this leads to «individual or group ethics» being displaced by «a tough corporate pragmatism; if they were not, the National Health Service would cease to operate» [7]. Or when the notion is put forward that scientific ideas on the human genome will lead to a situation in which it is no longer valid to use «the abstract concepts of good and evil» and where it would instead «be easier to stand on the ground of utilitarianism and employ the criteria of public well-being and benefit» [8]. The problem of course is how to justify the «corporate pragmatism» alluded to in the first case or the «public well-being and benefit» invoked in the latter. Clearly, these are two questions typical of ethics.

2.5. The fifth error, and certainly one not attributable solely to scientists and jurists, consists of replacing ethics with ideology, or, put more clearly, rational ethical discourse with invocations of high-sounding words that if not minimally specified have only emotive significance. For example, not much is said by the statement that the norm guiding the human genome study programme consists of granting «absolute priority to human rights and the common good»; or that in order to contribute something to the debate regarding genetic diagnosis in early pregnancy one must be «firmly committed to individual rights and human dignity and should openly accept a free society of pluralistic values» [9]. The proof that such statements say nothing is that they are impossible to refute; nobody would be willing to affirm the contrary proposition.

2.6. The sixth error is to confuse ethics with religion. Obviously, the moral ideas of many people are rooted in religion, but this should not lead us to identifying the one with the other. Expressed in terms common to the philosophy of science, in a universalist and rationalist conception of ethics, religion properly belongs to the realm of discovery, not to the realm of the justification of ethical or scientific theories. Hence the absolute vapidity from an ethical or scientific standpoint of statements such as: as «the fact that the Catholic Church considers the production of human embryos *in vitro,* for whatever reason, to be a violation of human

[7] Ibid p. 80.
[8] Ibid p. 104.
[9] Ibid p. 281.

dignity and therefore morally illicit makes any type of germ-cell therapy involving *in vitro* fertilization ethically unacceptable as well» [10]; or «the only mandated [by the Koran] form of procreation is that which stems directly from sexual union» [11]; or «the concept of *genetically* "inferior" races is... improper and unreasonable...[because] the book of Genesis tells us that God created only one Man (Adam)» [12]; or that in connection with «the inheritable alteration of cells and whole organisms... a stewardship of creation in this area leads to a conserving ethic and an ethics of restraint which takes into account the sanctity of the species, not just of the individual self» [13]; or «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» [14]. The ethical content of what is said or not said therein may be correct, but not for religious reasons. Religion plays no part in rationalist ethics; or, if you will, it plays the same part as it does in scientific investigation.

2.7. I believe declaring that one sees «the advances in molecular genetics supporting the value and uniqueness of the individual, not only because of the special nature of each genetic inheritance but because of the demonstrated uniqueness of each environmental interaction [...] If each human is a unique product of gene and experience, then this reinforces our unique worth as individuals» [15] is a good example of the naturalist fallacy already denounced by Hume as early as the 18th century, which consists in passing from a descriptive discourse to a prescriptive or valuative discourse. For attributing greater or lesser value to the individual (as opposed to the collective?) is something which strictly speaking has nothing to do with molecular biology. Besides, I think there are enough grounds for maintaining we are genetically distinct –that is, unique individuals– as for making the opposite claim, given that «the individual differences of Human Genome are rather small in terms of its composition: 0.1% or ca. 3×10^6 base

[10] Ibid p. 125.
[11] Ibid p. 132.
[12] Ibid p. 140.
[13] Ibid p. 177.
[14] Ibid p. 180.
[15] Ibid p. 196.

pairs for two unrelated individuals» [16]. And continuing along such lines, in view that apparently «nearly 99 percent of the chemical information contained in our DNA cannot be distinguished from that of any monkey in a zoo» [17], we should perhaps conclude that if we wish to conduct ourselves ethically with respect to chimpanzees and gorillas (given their proximity to us), we would have to guarantee them a pension (which they could consume as food or other objects of pleasure) only slightly less than that accorded our retirees. Fortunately, of course, molecular biology is powerless in the face of logical arguments such as those wielded by Hume and, afterwards, by a fair portion of the moral philosophers who succeeded him.

2.8. The eighth error consists of confusing, in moral reasoning, factual arguments with normative arguments. I think that citing as an example the Carrie Buck case (in which the court authorized the sterilization of a person considered as mentally deficient) borders on committing this error. For the United States Supreme Court's decision in that case was flawed precisely due to a question of fact: Carrie Buck was not mentally deficient. The normative premise underlying the reasoning, that is, that mentally deficient persons can on occasion be sterilized may be very well justified from a moral standpoint. In fact, Spain's penal code, has recently –and fortunately– ceased to hold as punishable «the sterilization of an incapacitated person afflicted by serious mental deficiencies when authorized by the Judge at the request of the incapacitated person's legally authorized representative, upon hearing the findings of two specialists, and the office of the attorney general on the basis of examination of the incapacitated person» [18]. Assertions that «the idea that created the misfortune of Carrie Buck» and many other «tragic results» consists in that «human life can be guided by the realities of biological determinism», or that «moral and ethical agency is an attribute of people [of whom else if not?], not of science or the scientific method» [19] strike me as incomprehensible and I much doubt whet-

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[16] Ibid p. 93.

[17] The quote is translated into English from the Spanish edition of David Suzuki and Peter Kandston's *Genetica. Conflictos entre la ingeniería genética y los valores humanos* [Genetics. Conflicts between genetic engineering and human values], Tecnos, Madrid, 1991, p. 297.

[18] Spanish Penal Code, section 428 after the 1989 reform.

[19] Pages 163 and 164 of the Proceedings of the International Workshop on the Human Genome Project: Ethics, op cit.

her a person of such recognized intelligence as Supreme Court Justice Oliver Wendell Holmes, who delivered the majority opinion on that case, ever gave any thought to such outlandish ideas.

2.9. The ninth error consists in ignoring the fact that ethical principles –like legal principles– are *prima facie* by nature, that is, they do not completely determine the resolution of a case but rather furnish reasons in favour of a certain decision, and that they may be defeated by reasons emanating from other principles or rules. Moral argumentation, as argumentation based on principles, is therefore somewhat inconclusive and open –new circumstances may always arise which could upend the balance of reasons. But this does not mean that the principles per se are in continual flux. Investigation into the human genome does not alter the already classic principles of bioethics (beneficence, autonomy and justice, or the equitable distribution of scarce resources). What it does is raise new circumstances for the application of those principles. These new circumstances, in turn, should give rise to rules which, as opposed to principles, are specific guidelines that tend to completely –that is, without considering other reasons– determine decisions. Incidentally, it is only fitting to point out that these principles are nothing but the rediscovery of Kantian ethics (the three classical formulations of the categorical imperative), which not without reason has been the paradigm of a rationalist and universalist ethics, linked to the Enlightenment and Modern ages.

2.10. And finally, the last error (and partly stemming from the preceding ones) is to demand of ethics what it cannot provide: doctrine and not theory. Like scientists, ethicists have no legitimate claim vis-à-vis other people to any specific competence for the determination of right and wrong, of what is permissible and what should be prohibited. What they can do, and what they in fact do, is to elaborate conceptual and theoretical instruments which while perhaps never, or almost never, sufficient for attaining truths, can nonetheless help avoid many errors.

3. And speaking of errors, I would like to close by taking the precaution of acknowledging that some of the errors which I believe I have detected in others may actually owe to nothing more than misinterpretation on my part. Many of my assertions –necessarily dogmatic due among other things to

the demands of brevity– must find their support in complex and debatable reasoning. Nonetheless, I cannot help but think that meetings such as this provide me with a unique advantage: my ignorance of natural sciences, particularly genetics, is so thorough that I do not even consider myself qualified to commit errors.

MAN'S FREEDOM AND THE GENOME

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«Contrary to what we might believe,
it is not on the basis of biology that a true idea
of man can be formed. On the contrary, only on the basis
of an idea of man can we put biology at the service of the same.»

Gros, Jacob and Roger [1]

The human genome and scientific discoveries

1. Analysis of the question

As we have maintained on another occasion [2], never in human history have scientific discoveries so affected the essence of human beings as the discoveries now arising from the use of new biogenetic techniques [3].

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[1] Gros, F., Jacob, F. and Roger, P.: *Sciences de la vie et societé*. Cited by Augusto M. Morello in *Las libertades fundamentales y la ética*, Librería Editorial Platense, La Plata, 1992, p. 3.

[2] Banchio, Enrique Carlos: «El Derecho Civil ante las nuevas exigencias en la tutela jurídica de la persona human» [Civil law before the new demands for legal protection of the human person], *Anales de la Academia Nacional de Derecho y Ciencias Sociales de Córdoba* (Argentina). Tome XXX-Vol. 2, 1991, pp. 253 and ff. Also in *Las responsibilidades profesionales*, Librería Editorial Platense, La Plata, 1992, pp. 38 and ff.

[3] Barbero Santos, Marino: «Proemio» to the work *Ingeniería genética y reproducción asistida*, Madrid, 1989, p. XV. He insightfully comments: «The "to-be-

«When humanity reaches an unimaginable level of technical progress, when it has discovered the secrets of matter and plays with the forces enclosed therein, then man, considered as an individual person, is diminished as a subject of law and obligations. The world is becoming dehumanized, the rational being becomes a number, the universal and abstract absorb the human person...» [4].

Before such a juncture, law cannot ignore technological transformations nor disregard the danger that its hierarchy of values be recast on the altars of technical progress' exultant supremacy [5].

In this regard, the prodigious discoveries of the so-called «scientific boom», primarily in the field of the «new genetics», prompt perplexity in some and well-founded concern in others. Perhaps this owes in part to the fact that the use of these discoveries frequently leads to assaults not just on human dignity but also on nascent human life, pondered under the dehumanized scientific prism [6].

Science and technology thus form a dual legacy. On the one hand, they bring major immediate benefits; at the same time they generate the possibility of undesired negative consequences. It is known that in the current stage of technological development there exist alongside the unquestionable advances and progress new phenomena representing aggressions on the rights and liberties of man [7].

For the first time in history, «homo habilis» has attained the capacity to design life by means of deliberate human intervention

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in-the-world" transformed by the result of scientific advances become a radical recasting of the pure "being-in-the-world".

[4] Borrel Macía, Antonio: «Para una mayor humanización de nuestro Derecho Civil» [For a greater humanization of our civil law]. Admission address to the Academia de Jurisprudencia y Legislación de Barcelona, p. 16. Recalled by Díez Díaz, Joaquín: *Los derechos físicos de la personalidad. Derecho somático*, Ediciones Santillana, Madrid, 1963, p. 27, text and note no. 47.

[5] Speech by Quintano Ripollés, Antonio: «El Derecho, valor de la cultura» [Law, a cultural value], insert to the *Revista General de Legislación y Jurisprudencia*, March 1986, Editorial Reus, Madrid, p. 6.

[6] Banchio, Enrique Carlos: «Status Jurídico del nasciturus en la procreación asistida» [Legal status of the unborn child in assisted procreation]. Under the title «Los avanzes científicos y el asincronismo jurídico» [Scientific advances and legal asynchronism] we pointed out that the constant expansion of scientific and technical knowledge leads to the need for enacting special legislation. Such legal provisions are in practice drafted by specialists in the relevant field, not by jurists. As such, the drafters are more interested in obtaining their desired wider scope for manipulation than in maintaining a respectful congruence with the ethical and philosophical principles which formerly inspired our legal codifiers.

[7] Pérez Luño, Antonio-Enrique: «Intimidad y protección de datos personales. Del habeas corpus al habeas data» [Privacy and the protection of personal data. From habeas corpus to habeas data], in *Estudios sobre el derecho a la intimidad*, Tecnos, Madrid, 1992, p. 38.

(somatic and germ-line gene therapy). Such possibility and its implications are awesome, all the more so when considering that humanity lacks historic, social or cultural references to guide it through this unknown territory.

It has been rightly asserted that issues relating to the origin or end of human life are rooted in our cultural past. As such, raising them engenders controversies insofar as they stir the deepest strata of the human psyche and make it difficult to achieve objective, dispassionate solutions [8]. The seriousness of the questions leads to justified concern when biology and medicine's assault on the human person can be described as a «brutal charge» placing us in a situation in which man, in search of himself, does not find man [9].

2. *Ethical and legal limits*

The outcome of the tug-of-war between what is «technically possible» and what is «morally acceptable» will depend on whether man is considered to have been made in god's image, as a rational being, as an end in himself, or, rather, as a simple object for the application of a scientific design in which «biological fact» is divorced from «ethical values» [10]. We will apply this line of thought to the ethical and legal limits which should be established in connection with man's freedom, in order to control the implicit powers that all scientific advances presuppose. What is present here is the belief or perhaps conviction of science's unlimited progress. As opposed to this belief we put forward the humanist thesis that «technical Logos» must be guided by a criterion of «ethical rationality» derived from the fundamental principle that «the human person must never be treated as a simple medium» [11].

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[8] Gafo, Javier (Editor): «La eutanasia y el arte de morir» [Euthanasia and the art of dying], *Dilemas éticos de la medicina actual*, published by the Universidad Pontificia Comillas, Madrid, 1990, p. 9.

[9] Repetto, Germán: Quoted by Castán Tobeñas, José in *Humanismo y Derecho*, Instituto Editorial Reus, Madrid, 1962, pp. 122, text and note no. 3.

[10] Lacadena Calero, Juan Ramón: *Ingeniería genética y reproducción asistida*, op cit, p. 19. The Professor of Genetics at the Universidad Complutense (Madrid), after explaining that «bioethics» seeks to unite ethical values with biological fact, sustains that humanity is in urgent need of a new wisdom that furnishes it with «knowledge of how to use knowledge» in order to achieve man's survival and improvements in the quality of his life.

Wils, Jean-Pierre: «¿Fin de la dignidad del hombre en la ética? [The end of the man's dignity in ethics?], in *Concilium*, no. 223, Madrid, 1989, p. 415. Referring to the debate over human dignity as it relates to the issues of genetics and euthanasia, he maintains that the result depends on whether man is understood as the image of god, as a rational being, or as the object of a utilitarian calculation for the maximization of pleasure, two antithetical conceptions.

[11] Belleli, Alessandra: «Aspetti civilistici della sperimentazione umana», Publication of the Institute of Private Law of the University of Rome, Cedam, 1983, p. 39: «It is noteworthy that the opposition between protection of the human

The ethical-legal problems raised by modern science require a clear definition of the ethical parameters essential for safeguarding the fundamental rights of the individual. This is seen in the questions posed to the 1985 Bioethics Colloquium by the president of the French Republic, François Mitterand, part of which we quote:

«None of our so-called developed societies, before the advances of science, can avoid reflecting on the values on which our identity is based. In essence, the history of the Rights of Man which rightly inspires so many passions is the history of a conquest, the idea of the human person. What is to be done, then, when this notion of person can be altered by science? What becomes of the also fundamental concepts of life, death, parenthood?» (*Le Monde*, April 24th 1985) [12].

What is at stake –it has been correctly observed– is the identity of the human person, founded on the difference between the sexes, in the order of generations, and in the sacrosanctness of the human body [13].

The intervention of lawmakers within a free system –indisputably upheld as the most favourable system for the progress of scientific investigation– should draw its inspiration from the root principles of human nature which lead to the safeguarding of the dignity of the individual human being, who, as an end in himself, is not susceptible to being treated as an object of scientific investigation.

Today, man has in his hands the power to control his genetic evolution. This capability calls for a great sense of responsibility, premised on the notion that not everything that is possible is at the same time licit or humanizing [14].

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person and the progress of scientific investigation in the medical field would be better assured by an adequate preventive system to control and coordinate research activity than by a repressive system based on the principles of civil and criminal liability.»

[12] Varaut, Jean-Marc: *Lo posible y lo prohibido*, translation to Spanish by Rosa S. Corgatelli, Editorial Atlántida, S.A., Buenos Aires, 1991, p. 131, Note no. 1.

[13] Varaut, Jean-Marc: ibid, p. 13. He formulates the warning that «cloning is the horizon of the idolatry of technique described by Heidegger. The clone is an organ copied exactly as is, immunologically identical... And what has been reproduced will no longer be similar, it will be the same. It is known that the reduction of the other to the same is the horizon of all spiritual, political and scientific totalitarianism. Technology which deprives the child of the right to be born as a unique being is altruicidal.»

[14] Gafo, Javier: «Problemática ética de las nuevas formas de reproducción human» [Ethical problems of the new forms of human reproduction in] in *La Fecundación Artificial, Ciencia y Etica*, Editorial Covarrubias, Madrid, 1985, pp. 77 and ff.

Analyzed contemplatively, the phenomenon acquires a crucial character, because it closely affects man's self-comprehension [15] and the limits which may be set forth should not close off the path of scientific knowledge, for the latter is a heritage of all humanity. Opposed to the position of accepting no limit other than that which is «technically impossible», a thesis is put forward that «technical Logos» must be guided by a criterion of ethical rationality: «the human person must never be treated as a simple means» [16].

Fixing limits that can avoid the clash between interests protected by law, which must not be left to the discretion of the ever more pressing research and experimental demands of modern scientificism, does not appear to be an easy task, nor to offer promising results [17]. The dialogueetween scientists and moralists is not always coherent and sometimes appears to be conducted by people speaking different languages, or «reasoning with incompatible logics». Mutual reproaches frequently arise, possibly deriving on the one part from the moralists' social responsibility and, on the other, from the scientific value of these practices for genetics, embryology, and medicine itself, all governed by the iron logic of research [18].

Thus, while some look to ethics for guidance in the face of the threat represented by biotechnological advances, there are those who think that ethics will do nothing but fog the scientific outlook [19].

As an epilogue to our line of reasoning, we point out that lawmakers must act in this area in order to prevent uncontrolled recourse to these techniques from leading to undesirable and possibly irreversible and dangerous consequences for society.

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[15] Lombardi, L.: «Las biomanipulaciones: Cuestiones éticas y jurídicas» [Biomanipulations: Ethical and legal questions] in *Persona y Derecho*, no. 15, 1986, Universidad de Navarra, pp. 85 and ff. In the author's opinion, «the problem is quantitatively, politically and economically minuscule...and, nonetheless, contemplatively crucial, because it closely affects man's self-comprehension».

[16] Rodríguez, Luño, Angel and López Mondejar, Ramón: *La fecundación in vitro*, Ediciones Palabra, Madrid, 1986, pp. 157 and ff.

[17] Lyons, David: *Etica y Derecho*, Editorial Ariel, S.A., Barcelona, pp. 17 and ff, 1986.

[18] Berg, P.: «Dissection and reconstruction of genes and chromosomes», *Science*, 213 (1981), pp. 296-303, as recalled by Rodríguez Luño - López Mondéjar, «This attitude could owe to the scientists understandable but unjustifiable impatience to achieve a prestigious personal satisfaction, which could be temporarily held up by the slow work of the legislator or the overly analytical and abstract work of moralists», op cit, p. 72.

[19] Rodríguez Luño, Angel and López Mondejar, Ramón: Op cit, pp. 9 and 10.

Modern genetics versus freedom as a supreme human value

Inquiring into the conflicts which can arise between modern genetics and freedom as a supreme human value, it is absolutely necessary to make (at least succinctly) a preliminary reference to the function of genes in the hereditary processes of cells, and to the possibilities of their control.

«A gene is the way in which life remembers how to perpetuate itself. This memory is chemical. It is interlaced with the intricate internal structure of a family of biological molecules, called nucleic acids, found in chromosomes and other of the organism's gene-carrying bodies, from viruses and bacteria to human beings. The nucleic acids are called deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

«Genes are the vehicle of biological inheritance: the means by which living beings transmit genetic information from one generation to another. They are the organizational principle by which lifeless raw materials are almost miraculously transformed into living organisms: they are absolutely essential to life» [20].

With these elemental concepts as a starting point it is not difficult to see the sweeping power inherent in genetic research and knowledge, which more than any other science penetrates into the depths of human intimacy and identity.

The inviolability of the human genome

Genetic manipulation of somatic cells (those which make up the person's body as merely temporary structures that disappear with the person) may fall into the sphere of personal decision.

Conversely, genetic modification of human germ cells (plasma forming an independent, potentially immortal tissue) requires the consent of all members of society insofar as it compromises the future of human progeny, and thus requires explicit prohibition [21].

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[20] Susuki, David and Knudston, Peter: Op cit, p. 25. [The quotations given here and in the following footnote are translations from the Spanish version] Recall Lewis Thomas's opinion (in N. Tilev's Discovering DNA) when he maintains that nature's greatest achievement was to create the DNA hidden in the interior of the first cell, of the membranes, and of everything else, in some part of the primal soup which covered the planet while it cooled.

[21] Ibid, pp. 160 and 184. «The application of genetic therapy techniques only to somatic cells –cells of the bone marrow, liver or brain, for example– could protect us from errors, given that these cells are mortal. Since the somatic

This distinction strives to mark a qualitative barrier between that which may be done in other animal species and that which from an ethical standpoint is unacceptable in human beings.

Intervening in the most intimate biological redoubt (genome) makes Man into Lord over his own evolution, but deprives the human person of the right to be himself, to come into the world without his traits having been programmed or prepared by the wishes or interests of others.

This argument has served as a basis for asserting that «it should not be attempted to engineer specific genetic traits in the germ line of the human species» [22]. The role of Law, in keeping with the ethical dimensions of the issue, should as a fundamental principle safeguard the genetic inheritance of our species' germ line, proscribing techniques involving surgery on the human genome [23]. In the face of the growing threats, voices have been raised saying that the time has perhaps come for the human genetic inheritance of individuals, as well as of populations, to be declared the inviolable result of a long evolution in which it would be reckless to introduce sudden arbitrary changes [24].

Others hold the opinion that gene therapy techniques applied to human germ cells imply the determination of the new being's traits by the parents. «Such human improvement profoundly contradicts human dignity and general human rights». In particular, the existential freedom of the person born in such conditions is vitiated [25].

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cells do not outlive the human organism, the problems caused by errors or poor calculation in genetic repairs are probably limited to the life of the patient subjected to the treatment. Our individual and collective ethical judgements should reflect this profound biological difference between somatic cells –with their short-lived genes that fall in the moral domain of individual decision– and germinal cells with their potentially immortal cells, about which future generation, from the moral standpoint would also have something to say».

[22] Resolution undersigned by 56 religious leaders (including Protestant, Catholic and Jewish representatives). Congressional Record of June 10th 1983. Quote taken from the authors and work cited in the preceding footnote, p. 160.

[23] Human genome is understood to be all gene-carrying DNA sequences (deoxyribonucleic acid) contained in a human cell (the individual's complete genetic makeup).

[24] Abrisqueta, José Antonio and Aller, Vitalino: «Directrices éticas de la manipulación genética» [Ethical guidelines for genetic manipulation], *Fundamentación de la bioética y manipulación genética*, edited by Javier Gafo, Publications of the Universidad Pontífica Comillas, Madrid, p. 193, 1988.

[25] Gafo, Javier: «El nuevo "Homo Habilis"» [The new «Homo Habilis»], *Ingeniería genética y reproducción asistida*, edited by Marino Barbero Santos, Madrid, p. 165, 1989. The author illustrates: a cloned offspring would be a being whose authenticity of being himself, whose freedom to discover himself have been asphyxiated [...] This diminishes a fundamental right which unavoidably pertains to existential freedom. P. 168.

If respect for human dignity constitutes an ethical category and becomes posited as a principle of law, any transgenic intervention which impedes man from unfolding and fully realizing his very own humanness would be illegal [26].

It has also been declared that the cost to humanity of being unaware of certain genetic processes could become unacceptably high when it is considered that genetic manipulation could potentially multiply biomedical errors exponentially. The unfavourable results would outlive the gene therapist and the patient who gave his consent to the genetic intervention [27].

Responsibility as the shadow of freedom

And we say the intervention of law, in an area that becomes intractable to its application, precisely because it is tied to man's freedom. We thus recognize the permanent bearing of the principle which, with the force of a moral imperative, reminds us that for so long as freedom is illuminated by the light of law, it will project a shadow: the shadow of responsibility.

The «responsibility principle», a cornerstone of our culture, could eventually be banished from our conscience and rendered hollow by the manipulation of human reproduction [28]. The interplay between the rights emanating under law and the duties imposed by responsibility make up the «ethical code of responsibility», which manifests itself in troublesome present-day issues such as the use of nuclear energy, degradation of the biosphere, genetic technology, etc, and serves to orient man's conduct within a process of sustained cultural impregnation [29].

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[26] Schüller, Bruno S. J.: «La problemática de la ingeniería genética desde la perspectiva de la teología moral» [Problems of genetic engineering from the standpoint of moral theology]. Translated into Spanish from German by Antonio Zubiaurre. *Ingeniería genética y reproducción asistida*, op cit, p. 223.

[27] Ibid.

[28] Peterson, Peter: «Medicina de la reproducción: un desafío a la actitud científio-médica ante la hominización» [Reproductive medicine: a challenge to the scientific-medical outlook and hominization], *Ingeniería genética y reproducción asistida*, op cit, p. 51.

[29] John Paul II: In a call for wisdom and the ethical conscience which should guide the use of the powers implicit in scientific discoveries, contained in his talk «Address to participants in the International Medical Congress on prenatal diagnostics and surgical treatment of congenital malformations» (December 3rd 1982) affirmed: «One of the greatest risks to which our age is exposed is the divorce between morals and science, between norms of ethics and the possibilities offered by a technology contemplating ever more fascinating horizons [...] It is necessary for all responsible persons to agree to assert the priority of ethics over technique, the primacy of persons over things». See: «Bioética y Moral Católica» [Bioethics and Catholic Morals], *La*

This demand for responsibility as an ethical category which the scientific *novum* must confront grows proportionally to the increased power intrinsic to all scientific knowledge [30]. We have maintained that this spectacular technological progress demands an extraordinary sense of responsibility due to the pressing need for protection from potential hazards and incorrect wayward developments. Nevertheless, it would be wrong to reject all the new possibilities ushered in by biotechnology, and in particular by the «new genetics», because of supposed anxieties or ungrounded fears [31].

Conclusion

As a corollary to the above analysis, we believe that the principle of freedom, in this case, the freedom of the researcher or genotherapist, is not absolute, but must be coupled with the principle of responsibility, which as an ethical category limits all interventions entailing possible harm to the eminent dignity of human beings. The latter value cannot be relegated to a lower position on any valuative hierarchy, for it is the essential value at the core of human existence, understood as a goal in itself [32].

Biología frente a la Ética y el Derecho, Publishing Service of the University of the Basque Country, San Sebastián, p. 48.

[30] Gafo, Javier: Op cit, footnote 25, p. 166. Referring to the ethical category of «responsibility» the author insightfully points out that in the past ethics focused on respect for the rights and interests of other men; but today it is the biosphere which is at stake, with its millions of species that could be gravely menaced by man's irresponsible intervention.

[31] Eser, Albin: «La medicina moderna en la reproducción e ingeniería genética - Aspectos legales y sociopolíticos desde el punto de vista alemán» [Modern medicine of reproduction and genetic engineering - Legal and sociopolitical aspects from the German standpoint], *Ingenieria genética...*, op cit, p. 295.

[32] Kant, Emmanuel: *Fundamentación de la metafísica de las costumbres* [Foundations of the metaphysics of customs], Espasa Calpe Argentina, pp. 91 and ff, 1946.

FREEDOM AND THE NEW GENETICS

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Introduction

The rapid advances in human genetics which have coalesced into the Human Genome Project (the New Genetics) hold promise for increasing knowledge about the biological component of human states. For those traits which are involved with human illness and suffering, the New Genetics may suggest novel palliatives or possibly curative therapies. But the vast majority of data to be generated will be relevant to normal processes. Alterations of human characteristics affected by genes –the functioning of the immune system, stature, aspects of consciousness or mental processes– are being attempted. Irrespective of challenges that such a experimental program poses to traditional notions of personal liberty, and the eugenic implications of these inevitable applications, genetically based manipulations of humans will alter concepts of «normalcy» and the «individual». These notions are key to protecting personal freedoms and setting the appropriate re-

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lationship between citizen and state. The laws and traditions which protect individuals may need to be retooled.

The United States tradition

In the United States, founding documents state that it is «self evident» that «all men are created equal». It has taken about 200 years to expand this belief (as opposed to a biologically proven *fact)* to include women and non-caucasians. But the Founders were not geneticists; the New Genetics demonstrates that we are not all equal but rather definitively genetically distinct, though groupable by general or specific inherited similarities. Should the law then emphasize our equality despite scientific findings or simply adapt to our growing realization of inherent difference?

The Bill of Rights was crafted in order to protect the individual from the newly created and powerful state. Various freedoms including the right to gather, speak and write, practice religion, bear arms and have access to impartial justice were enumerated in order to fashion a society where the search for «life, liberty and the pursuit of happiness» might have a chance of success. Though privacy was not specifically mentioned, several amendments address its aspects, and the jurist's view that Americans feel they have the «right to be left alone» accurately reflects popularly held views.

But technology and medically focused applications of basic science are forcing a reevaluation of this tradition. If by transplantation we replace most or all of the major organs, by somatic or germline genetic manipulation change some or most of the genes in portions or all of the cells within our bodies, then are we dealing with the same individual? Is that person's previous history and interaction with the state relevant? Do rights to property or responsibilities to uphold contracts persist? Does the individual entitled to the dignity and rights spelled out so clearly by the Founding Fathers exist distinct from his or her manipulatable biological component?

Though these are basic questions, the situation is in fact more subtle. The current system operative in the United States, if left unmodified, makes entitlements such as access to healthcare, familial financial security, owning a home, adopting a child or achieving at school or in the workplace (particularly in unpredictable ways) possibly contingent on taking predictive genetic tests and having an acceptable «type». What becomes of common notions of privacy and the «right not to know» something about ourselves *(knowing* in this context meaning something that you are both conscious of and which prompts stigmatized responses from the

local environment), if such basic entitlements and benefits of citizenship are contingent on testing-subordinated to a business ethic? It becomes arguable that our most important evolutionary development, human psychology and self-consciousness, becomes less effective as an adaptive and creative tool when a society or government dictates what we must face and know about ourselves, our parents, siblings and children in order to retain our rights.

Research efforts

For those engaged in the study of the social impacts of the New Genetics, these questions represent a kind of Rubicon-daunting, elusive, seemingly unanswerable in an unbiased manner. But recent work of my collaborators and I, investigating the lives of those experiencing genetic discrimination in the United States currently, may help suggest answers. After four years of study and hundreds of interviews, the data clearly suggest that:

1. Genetic discrimination defined rigorously as solely arising from *genotypic difference,* or more sensibly as *discrimination based on genetic information in a particular setting,* exists. In fact, many individuals who deny experiencing genetic discrimination have adapted to the environment where it takes place and avoid the generation of personal genetic information.

2. Genetic research and information can not be seen as independent of the social, political, cultural and economic realities in which they are generated and applied.

3. Respect for human variation, compassion towards difference, and significant investment in applied genetic research and services are essential to abrogate genetic discrimination.

4. Laws, policies, and determined organized political activity to combat the misuse of genetic information will be necessary but not sufficient to limit genetic discrimination.

Yet, there may still be hope in interpretations of the Founder's intentions. The individual in the Constitution of the United States transcended genes and biology; the protected being existed pre-science. By reenforcing classical notions of individual freedom, civil rights and exposure to a limited participatory government, some safety may be derived. Vigilance to every unsupported claim and extension of the science of genetics into social engineering (whether directly or by way of Professor Troy Duster's «back-

door»), protects us from a powerful science and insures that its benefits will outweigh the problems generated.

Conclusion

The study of genetics is the examination of difference which can be attributed to genes within a specific environment. Even sequence information is functionally uninterpretable when taken out of its environmental context. Adverse genetic discrimination is an inevitable outcome of the application of genetic information in societies and locales where stigma, prejudice and frank repression are already prevalent. Intolerance of difference, the desire for social homogeneity, the hubris of the majority are all both anti-genetic and the fertile soil for misuse of genetic information. If the New Genetics is accompanied by a careful and systematically applied universal restatement of the rights of humans then generations to come will note that we produced data showing a linkage between genetics and freedom.

But we may fail to create this legacy –this cultural/political genetic linkage– and fall into another age where divisiveness, ethnic hatred, social failure and civil strife are conceptualized and approached as genetic or biological issues. If this occurs, then the New Genetics may only help create banks of private data, designer camps or neighborhoods of genetically similar people, and lives dictated by the myths of genetic determinism and inevitablism. Such an outcome, as opposed to progress leading to freedom, hope and greater fellowship of humankind, is unacceptable to this geneticist.

FREEDOM AND THE HUMAN GENOME

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Primitive curiosity for the world

This is not the occasion to recount the history of human attempts at self-discovery throughout the ages. The subject is nevertheless enthralling and the idea of surveying the history of humanity's quest to discover the as yet unfathomable mystery of human nature retains its allure.

Historically, man was primarily preoccupied with his outer surroundings, with the objects which served him to subsist and to improve his wellbeing. Throughout the centuries human energies went into domesticating plants and animals and taming nature. Imagine the pleasure felt by primitive man when he rubbed two stones together to make fire. Fire attained a divine category in a world where almost everything was yet to be discovered.

Human curiosity is insatiable and unlimited. At first, and for centuries, it was directed at the world in order to know it and thereby put nature to work for man's benefit. All the necessities of life could be found in nature. So pressing was the struggle for survival that human beings probably had neither the time nor the means for pursuing the discovery of their own nature. All impenetrable mysteries were attributed and transferred to deities in possession of total power over man and destiny.

In primitive times, the gods were not abstract beings. They were incarnated in those object which most impressed humans: the sun, moon, stars, mountains, and certain animals such as the jaguar, bull, and serpent, to name but a few. Sensory perception was the main avenue to knowledge.

Metaphysical siege

When did man begin to turn his gaze inward, to reflect on his own being? In our civilization it was Christianity which made clear reference to the nature, conduct and destiny of human beings. Realist religions and various prevailing animisms were left behind as humanity came to know an abstract, single, tripartite, omnipotent and merciful god whose message was centred on love.

Christianity began to dispel the mystery by means of revelation. Man was made in the image and likeness of God, and partakes of him. God is in man, and in nature, which thereby acquires a sacramental value. God also resides in a sidereal realm whose space and time terms we cannot even begin to imagine.

Irrespective of the values provided by Christianity and of the faith its message may or may not inspire, what is noteworthy for our purposes here is that they represent a decisive contribution to the knowledge of human nature, without completely unravelling the impenetrable mystery contained therein.

In my opinion, the most important idea forthcoming from Christianity in this respect –apart from positing love as the central value of human existence– was to regard man as an ontologically free being. Through its teachings we grasped that were it not for free will, man would lack the capacity for salvation or perdition. Without human freedom, neither Christianity nor human existence itself would have any meaning.

This general assertion certainly raises problems and invites challenges. Recall in this regard the debate between Saint Augustine and Bossuet over the scope of human liberty vis-à-vis the probable intervention of God in his life. The metaphor of the clock to which the said philosophers likened our existence is sufficiently illustrative of this debate on the constraints on human freedom in relation to the Divinity.

One position held that God only wound up the clock to set it into motion; that is, the deity was only responsible for creating man endowed with the necessary freedom to decide his own salvation or perdition independently of God. The other side ar-

gued that God's intervention was not limited to only starting up the clock, but could act to set the clock back or forward should any mishap occur; otherwise, what would be the value of orations? I will not enter an opinion on this debate, but only point out that the issue exists from a theological standpoint.

Christianity's profound yet simple teachings on man and his human liberty suffered, in my opinion, certain philosophical misinterpretations which confused the message's original essence with secondary or accessory aspects. This often led to the core of the message being overlooked. There are specific writers and philosophical schools which can be cited as having created confusion on this subject. It is to this situation that we may attribute the resulting eclipse of the most important and valuable parts of those teachings. I believe that an understanding of human nature has been hindered, not helped, by the heated and still unconcluded debate over whether or not essence precedes existence. I make this assertion fully aware of its many philosophical implications and admit the always present risk of error that accompanies all human reasoning.

The quest for an essence, for a being underlying things, in all things, is what made metaphysics the central concern of philosophical schooling. Philosophers sought to explain the world by grasping the «being» of objects, of that which received the apt name «metaphysics». For the Greeks, observed Heidegger, from the exegesis of being «there develops a dogma which not only regards as superfluous the question as to the meaning of being, but moreover sanctions the omission of the question». They held that «being» was «the most universal and empty of concepts», according to Heidegger. Hence the conclusion that not only did the question as to being not have an answer, «but that question itself is obscure and lacks direction» [1].

In addition, in their definition of human beings some thinkers and their followers stressed, as had Boecio before them, that man was an «indivisible substance of a rational nature». While true –who could doubt it?– such an assertion, which avoids the question of existential freedom, inexorably leads to limitations or distortions of an overall understanding of human nature. How can freedom be disregarded when referring to human beings? How can human beings be reduced to the rational only? Boecio's definition, passed on over the centuries, made us lose sight of the most essential element of man: his existential freedom.

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[1] Heidegger, Martin: *El ser y el tiempo*, Fondo Cultural Económica, translated into Spanish from the German by José Gaos, Mexico, 1951, p. 6. (All quotes have been translated into English from the Spanish version.)

Centuries passed before Boecio's correct but insufficient vision of human beings could be overcome. It was early in the 20th century, though visibly rooted in the preceding century, when a renewed interest in man's being was kindled. Philosophers on existence such as Heidegger, Jaspers, Sartre, Marcel and Zubiri, in varying ways became the architects of a profound and fruitful rethinking of an issue of cardinal importance to man. It is to them that we owe the first philosophical discovery about human beings. For the first time existence was equated with freedom.

Man reflects on his being

I believe and have already stated that the task of the philosophy of existence is to reflect on medullar issues of mankind which form part of Christian thought, though this was not necessarily the intent of the thinkers of this school of philosophy. Obviously we cannot forget that the conclusions reached by some of the thinkers of this school, such as Sartre and Heidegger, had little in common with the Christian message.

Thus, neither Sartre's «being-for-nothing» that escapes in the future, nor Heidegger's «being-for-death», whose existential odyssey concludes quickly and definitely, bear much relation with the «being-for-transcendence» which illuminates the Christian faith and that is based on hope, so dear to Marcel.

Kierkegaard perhaps initiated this fruitful and enriching stage of philosophical reflection on man, which Descartes joined with his own outlook. But it was during the years between this century's ferocious world wars that a seminal philosophical movement took shape. It was in that period when the philosophy of existence blossomed in all its vitality.

I view the philosophy of existence as representing a major revolution in the history of philosophy. Prior to the emergence of this new way of approaching philosophy, human reflection, as already stated, centred on the outside world. Beginning from the moment when the horrors of war spurred man to turn his inquiring gaze inward, a major advance was made in our knowledge of this mysterious being we call man.

As stated, the contributions made by the philosophy of existence to deepening and complementing the view of man held by Boecio and his followers constitute a great –and undervalued– revolution in the «discovery» of human existence.

The first discovery of human being

In his 1844 book *The concept of anguish* [2], writing on the question of original sin, Sören Kierkegaard describes his work «as a simple psychological investigation» of the subject, adding that his purpose was not «a pompous philosophical investigation».

Kierkegaard concluded his reflections by stating that man «is a synthesis of soul and body» [3]. Up to here he was repeating what was already known to those who used their faith to ponder their own being. Worthy of our attention, however, are the words with which he completed the above-quoted line: he holds that the said soul-body synthesis is «constituted and sustained by the spirit». We may venture to say that when using the term «soul» he was referring to the psyche. But what then does Kierkegaard mean by «spirit»?

The answer, in my opinion, is to be found a few pages further ahead where he explains that man by «turning inward, also discovers freedom». This freedom is seen by Kierkegaard as a «blessing». Freedom is not –and herein lies the importance of his work– «to attain this or that in the world, to become king or emperor or spokesperson of the age, but the freedom of being aware that today he is freedom» [4]; a freedom «that is never mere possibility –as soon as it exists, it is real» [5]. Freedom thus emerges in all its splendour as the central issue of contemporary philosophy.

As for the soul and body, and the spirit that sustains them, Kierkegaard believed the body to be «organ of the soul and, therefore, of the spirit also» [6]. The «spirit» appears anew as something distinct from the body and soul in which it «is found» and which it sustains. We gather that this spirit, discovered by man upon «turning inward», is freedom. Thus the essence of man is his existence. And existence «is» freedom.

The new philosophical winds began to dispel the conceptual mist shrouding this subject and allow us to glimpse that our existence is rooted in and draws its essence from freedom. These profound reflections opened up new way in the arduous path to the «discovery» of man as «subject» and not as a mere «object» seen from outside. This marked the beginning of the first great revo-

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[2] Kierkegaard, Sören: *El concepto de la angustia*, Espasa-Calpe, Buenos Aires, 1943.
[3] Kierkegaard, Sören: op cit, p. 89.
[4] Kierkegaard, Sören: op cit, p. 118.
[5] Kierkegaard, Sören: op cit, p. 26.
[6] Kierkegaard, Sören: op cit, p. 149.

lution in this realm of ideas, the onset of a new stage in man's relentless, perpetual and unfinished drive to discover himself.

Freedom as the focus of human attention

The trail blazed by Kierkegaard was later followed by other writers. But three quarters of a century were to pass before a new and unprecedented stimulus was to arrive and spur philosophers to reconsider, with new nuances, Kierkegaard's thought. This time, however, it was not original sin but the barbarity of war which compelled the more eminent thinkers to travel anew along the trail begun by Kierkegaard. In view of the results obtained I think it was worth the decades-long wait. Philosophical findings about man's existence, the close study of his being, would have vast repercussions on contemporary thought. One of them nourished the legal thought and jurisprudence of the second half of our century. The December 10th 1948 Universal Declaration of Human Rights furnishes telling proof of this assertion.

In this incessant search for what is human, Kant's vigorous thought cannot be ignored. Kant set down an important milestone in the path to be followed by contemporary philosophical thought. Suffice it to recall in this respect his conception of the person as «freedom with independence of all types of mechanism». The principle that man is an end in himself and not a mere instrument has been accepted as the conceptual mainstay underpinning contemporary legal science and legislation.

The central theme of the symphony of philosophical thought on human beings was now freedom, no longer just reason. It was discovered with unprecedented lucidity that to understand metaphysics, to grasp the being of all things, it was first necessary to know the «being» of the cognizant subject. Leading thinkers trained their scrutiny on man himself, who after centuries had thus become the central issue of knowledge. Pushed out of centre stage were the world and things, which had held the prime interest of the philosophers prior to the advent of the philosophy of existence.

It was Heidegger who put forth that before we could inquire about the being of things we must first conduct an exposition of human existence and being, of *dasein* as *existenz*. According to Heidegger the examination and interpretation of things would come later. The first part of his proposed plan is contained in his book *Being and time* [7]. He would never get to the second part.

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[7] See footnote 1.

The philosophy of existence marked a momentous turning point in philosophical thought. Philosophy's new preoccupation with man extended to other disciplines and signalled not just a way of thinking but a complete outlook on life. As Bobbio was to say, the philosophy of existence is no longer the opinion of a German philosopher or a French artist: it is «a way of philosophizing which strangely and wonderfully fits the philosophical vocation and, I would even say, the philosophical taste of our age» [8].

Sociology and law, among other disciplines, took up this position and thinkers came forward basing their scientific advances in the findings and contributions of the philosophy of existence. The implications for law were clear; the new advances exposed the limitations of the previously dominant individualist and patrimonialist conceptions. The response to these limitations was not to deny them but to affirm the centrality of the person in the jural world. There thus arose legal personalism as a feasible response to the central question of law.

Existence as freedom

Is it possible to define freedom? Much the same as Jaspers, I believe freedom is indemonstrable and hence undefinable [9]. Nonetheless, we feel and live the freedom that each of us represents.

The cognitive path for approaching freedom, understood as man's very being, is not «ontognosis» –rational, theoretical apprehension of man. Rather it is what Miró Quesada termed as «ontostesia»– an emotional state, such as love, hate, anguish, or despair, that is, a sensibility of being [10]. Rational apprehension of being requires distancing ourselves therefrom so that we may know being from without, as any other object subjected to analysis. In order to grasp freedom we must enter into direct contact with freedom, feel it, live it. In other words, freedom is only revealed to us «from within» as a personal experience, through a process of internalization. Emotions, sensations, are experiences which reveal to us our own being. Conceptual theories can come afterward, after this extraordinary experience of freedom «is lived». Such experience occurs but a few times in a lifetime, according to Marcel in situations in which «something of real importance is

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[8] Bobbio, Norberto: *El existencialismo*, Fondo de Cultura Económica, Mexico, 1951, p. 17.

[9] Jaspers, Karl: *La fe filosófica*, Losada, Buenos Aires, 1969, p. 4.

[10] Miró Quesada, Francisco: *Ensayos, I (Antología)*, Imprenta Santa María, Lima, 1951, pp. 27-28.

at stake» [11]; that is, situations which cause man anguish as to the decision to be taken.

Anguish arises from the responsibility of a human being before a decision of transcendental importance in his life. According to Kierkegaard, Heidegger and Sartre and others, it is through anguish that one comes to apprehend freedom; freedom which has been imposed on man as «his responsibility».

In line with the above reasoning Scheler held that people are not exclusively logical subjects, characterized by rational or wilful acts, but rather that an individual is the concrete reality in which such acts find their fulfilment [12]. For Scheler –much like Kierkegaard– a person is the «centre of the spirit», which presupposes «independence, freedom or essential autonomy –or the centre of his existence– confronted with the ties and pressure of the organic world, of life, of all that pertains to life, and, therefore, also of his distinctive intelligence» [13].

All the foregoing leads to the conclusion that spiritual being, which «is freedom», is individual, real, possesses existence and is temporality. It is an unfolding, a process. It lacks substance, notwithstanding which it is equivalent to itself. Freedom, as Zubiri pointed out, is the ontological situation of he whose existence rests on his being [14]. Freedom is neither an attribute nor a property of human beings. It is their very being.

Existence as freedom implies that we are before a being, an I, in constant motion, in the process of making himself, of writing his own unique biography. Because he is free, man charts out projects he may or may not fulfil. Thus, he is labile, projective and creative. In Zubiri's words a person carries out his «self-realization through the complexity of living» [15]. To do so man incorporate values into his life, permitting him to decide preferences, make choices and then plan. Man is thus an estimative being.

As can be seen, not only does the philosophy of existence show existence to be freedom, but as I will explain further ahead, it also paved the way for a reconciliation of the philosopher's position with the findings of science.

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[11] Marcel, Gabriel: *El misterio del ser*, Ed. Sudamericana, Buenos Aires, 1953, p. 298.
[12] Scheler, Max: «Etica» [Ethics], *Revista de Occidente*, Madrid, 1941, p. 42.
[13] Scheler, Max: *El puesto del hombre en el cosmos*, Losada, Buenos Aires, 1943, p. 131.
[14] Zubiri, Xavier: *Naturaleza, Historia, Dios*, Ed. Poblet, Buenos Aires, 1948, p. 390.
[15] Zubiri, Xavier: *Naturaleza, Historia, Dios*, op cit, p. 370.

Notwithstanding the above, and despite the great strides made in our understanding of mankind, our knowledge thereof is completely insufficient. Man remains a mystery to be deciphered, although his free, and hence unpredictable, nature leads us to believe that man will always see himself as a problem to be studied. His complex, rich and dynamic existential structure will ensure, as pointed out by Jaspers, that he is always more than what is known of him [16]. With his characteristic elegance, Mounier used an insightful metaphor to illustrate this situation when he said that «a thousand photographs combined do not make up walking, thinking, and loving man» [17].

The relativity of freedom

Freedom is not absolute. Insofar as he is free, man is able to decide on a specific life plan. This is the inalienable and original instance of freedom. But this decision, this plan, is made in order to be «lived out», and therefore requires its psychosomatic «casing», that is, a body, intelligence, will and sentiments through which it shall be manifested and act in the world. Man, though individual and singularly unique, is not enclosed in himself in isolation from the world. He lives in coexistence with others. He is a coexistential being [18]. Existence is coexistence.

Man is not cut off, constantly withdrawn inside his own «I». Being «in itself» is also «being with others». Both dimensions make up man's existential-coexistential structure. Man is individual and social at the same time. Jaspers pointed out that it is in communication and union with other men that existence finds itself [19]. Existence is given as communication.

In order to achieve self-realization as a free being the «I» must be able to rely on its psychosomatic entity, on others, and on things. Freedom is conditioned by the subject's own internal world, by his psychosomatic casing, by others, and by the things which surround him, all of which offer countless obstacles to the realization of each subject's existential project [20].

The «others» with whom man must necessarily coexist and whom he needs in order to affirm his own being may not acquiesce to his free decision. They may cooperate with the fulfil-

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[16] Jaspers, Karl: *La fe filosófica*, op cit, p. 5.
[17] Mounier, Emmanuel: *El personalismo*, Eudeba, Buenos Aires, 1962, p. 6.
[18] Fernández Sessarego, Carlos: *Derecho y persona*, Inelsa, Lima, 1990, pp. 73 and ff.
[19] Jaspers, Karl: *La fe filosófica*, op cit, p. 102.
[20] Jaspers, Karl: *La fe filosófica*, op cit, p. 58.

ment of his plan or impede or restrict its realization. Because he is thus dependent on «the others», man to be «himself» and must also avail himself of the things around him. All this relativizes, conditions or determines to some extent his freedom at the phenomenal instance. As noted by Mounier, absolute freedom is a myth from the moment of its limitation by the numerous necessities which constrain and by the values which prompt freedom [21].

The second discovery of man

As already indicated, being –which is the same as freedom– is first apprehended by means of «ontostesia». Through an emotional intuition, and a process of internalization, the freedom-radix manifests itself. This is the path proposed by the philosophy of existence for apprehending definitively and from within the «being» represented by each of us. Freedom is discovered through «anguish».

This contribution, which dates back only a few decades, has allowed us an increasing knowledge of mankind. But there is another path to the understanding of man. For centuries, mankind has been the subject of study by science, which explains man rationally, grasping him not «from within» but as an object to be analyzed «from without». In this sense, man has been studied by numerous disciplines, such as biology, anatomy, psychology, history, anthropology.

In the arduous and unfinished process of discovering man both the emotional and the rational paths have been and are used. They complement each other in contemplating this unpredictable and mysterious being of whom we know more each passing day yet as to whom all our knowledge is insufficient.

While the philosophy of existence represents a major turning point within philosophy, affording us a better understanding of existence as freedom, the parallel scientific revolution is currently represented by genetics. Although its roots reach far back into the past, it is in recent decades that this field has progressed with startling speed. Since Mendel's discoveries of 100 years ago genetics had not seen such an extraordinary qualitative leap forward as the one seen in recent times. Nevertheless, as we well know from what has already been glimpsed and is being predicted, genetics harbours even more astonishing findings for us in the near future. The Human Genome Project will represent the culmina-

[21] Mounier, Emmanuel: *El personalismo*, op cit, p. 6.

tion of a crucial stage in the understanding of the nature of human beings.

The results to be obtained from the Human Genome Project will bring enormous benefits. At the same time, however, the project also raises complex and delicate ethical and legal issues already visible to those directly involved in the process or who closely follow its progress. These issues must be studied as carefully, calmly and judiciously as dictated by the awareness that humanity's future is at stake. Genetics can oscillate between wonderment and terror, between good and evil.

The contribution and prospects of genetics

Just as the period between WWI and WWII was marked by the takeoff of philosophy insofar as concerns the «rediscovery» of the spiritual root of man's being, the year 1953 perhaps marks the moment which, thanks to Watson and Crick's findings on the helicoid structure of the DNA molecule, triggered the rapid advance in the field of genetics and, thereby, in the discovery of man's nature.

As everyone knows, the Human Genome Project undertakes to explore human nature by means of DNA analysis, to identify and precisely locate genes in relation to other genes, determine the exact distance separating them, and to thereby decode the message they contain; or what some scientists have metaphorically called DNA's «grammar of life», analyzing its component biochemical phrases, words and letters. The outcome of this extraordinary scientific enterprise, as proposed, will be to decode this biochemical information and obtain the so-called genetic map.

The mapping and decoding of biochemical information are goals which if fully achieved would in great measure allow us to complete the discovery of the nature of this «freedom being» called man. Their realization would clarify, in detail, the biological instrument at man's disposal in his quest for personal realization and the genetic determinants to which he is subject in the process of carrying out his existential project.

In principle, the Human Genome Project merits universal support as to its implications for our knowledge of human nature. It offers humanity incalculable benefits, particularly in the field of medicine. To be sure, many diseases are known to have a genetic component. The results thus far, and those yet to come, will permit more accurate diagnosis and, foreseeably, treatment of many of the diseases afflicting mankind. With the Human Genome Project

we have penetrated into a world most of which is yet to be explored. The question thus raised is whether it is possible to produce human proteins which can to some extent «cure» defective genes or replace missing ones. Recent experiments have yielded encouraging results and a positive answer to this question looks to be increasingly likely.

In the legal field, as is well known, genetics is already capable of furnishing evidence in cases where questions of paternity or filiation are at issue. It is also highly useful for the identification of criminals from hair, blood or semen traces [22].

We lack the scientist's information and vision perspective to be able to imagine other foreseeable benefits to be garnered from the Project, some of which we surmise will be wondrous. We are newcomers to what has been called the «virgin forest» of new genetics. Thus the «space» age is rightly starting to become known as the age of «genetic revolutions». I hope it brings benefits to the human race.

Genetics, ethics and law

Echoing some writers of recent years, I would like to point out the similarity between the possible risks generated by the Human Genome Project and those which arose from the discovery of atomic energy. As we know, all progress, all scientific advance entails not only potential benefits for human beings, but also an undeniable risk for humanity. Nagasaki, Hiroshima, Chernobyl, are names which now chill humanity upon each mention or remembrance. And nobody can assure us that other catastrophic events, predictable or otherwise, will not expand this roster of death and destruction.

In this regard Gerin has stated that the entire history of nuclear power «has raised enormous problems for governments and for jurists, problems which are still to be resolved» and draws the conclusion that «the consequences of genetic manipulation could entail consequences even worse than those of the atom bomb» [23]. Gafo has warned that «the major reservations stirred

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[22] In this connection, Max Arias Schreiber, in a recently published article in the daily *El Comercio* of Lima, reminds us of a famous 1986 case in Oxfordshire County, Great Britain, in which the police, after obtaining blood and saliva samples from more than 4,000 persons and applying the Alec Jeffreys method, was able to arrest a murderer. A similar case arose in Italy, where the police were able to track down the assassin of the famous judge Giovanni Falcone from his genetic fingerprint.

[23] Gerin, Guido: «El legislazioni europee in materia di ingegneria genetica e biotecnologia», *Modificazioni genetiche e diritti dell'uomo*, Cedam, Padua, 1987, p. 151.

by the development of nuclear power to some degree are applicable to this subject» [24].

Some premonitory voices have rightly called for further reflection and sounded a warning to prevent the potential disasters which could arise from misapplication of biogenetics and its fabulous achievements. Undoubtedly, the Human Genome Project generate delicate, complex ethical and moral issues, which must be sorted out swiftly and judiciously if we are to avert the harmful effects of a misuse of the knowledge genetics will foreseeably attain in coming years.

Multi-disciplinary groups should be organized to take up these questions, entrusted with the urgent task of anticipating, as much as feasible and with such precaution as is warranted, the possible disasters that loom in our near future unless we adopt the measures that reason and ethics counsel. Such an initiative, if backed by the leading scientific powers, could perhaps avoid the hazards and uncertainties that will arise for humanity as the Project yields more and more results of application in diverse scientific fields. It is imperative that the international community not be confronted with a fait accompli.

By the light of certain hideous and not-too-distant events it is not overly difficult to imagine some genetic engineer being tempted to try to «perfect» individuals by «correcting» their genes. An understandable misgiving and fear accompanies us when we think of the various consequence which could be unleashed by deviant eugenic applications of the results obtained by the Project.

The scientists participating in the Project, as well as those not directly involved and observers in general are not oblivious to the dangers and grave consequences, apart from eugenic ones, which could arise in the absence of an alert ethical consciousness. And for cases where such an awareness unfortunately does not exist, we must be prepared to move swiftly to devise the appropriate legal measures for safeguarding human beings against the threats and harm which could be generated by misuse of Project results.

Some of the aforesaid consequences have been already pointed out with due urgency by numerous scientists and writers, citing the grave danger of proceeding without an ethical sense. One of the most feared consequences (due to the ease with which it could come about) mentioned in recent years is that the right to

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[24] Gafo, Javier: «El nuevo *homo habilis*» [The new *homo habilis*], *Fundamentación de la bioética y manipulación genética*, Universidad Pontificia Comillas, Madrid, 1988, p. 222.

privacy could be affected. There exists the clear risk that the disclosure of genetic information, with its attendant violation of a person's privacy, could to some degree frustrate or limit the aggrieved person's possibilities of realizing his personal projects.

One of the issues most frequently cited in this regard is whether employers will require job applicants to undergo genetic screening, the results of which could obviously determine their employment eligibility. Another question which has scientists, and all people interested in the project in general, on edge is how insurance companies might conduct themselves in relation to the likely requirement that genetic profiles be established of its insureds. It is hypothesized that the said companies might not extend coverage to individuals with a predisposition to diseases of genetic origin.

Also of concern are the genetic manipulations or other misuses practised on unborn children whose genetic profile reveals a propensity for certain diseases. A prenatal diagnosis places the parents in the dilemma of having to make highly ethically-charged decisions such as whether or not to preserve the life of an unborn baby found to suffer a serious disease.

It is likewise possible to calculate the tragic effects for a person whose medical diagnosis reveals to him that he suffers from an incurable disease. Similar consequences would await all members of a family for which medical science diagnoses a disorder, such as Huntington's disease for instance, which has no medical treatment.

Thought has also been given to other situations relating to the issues before us here. The possibility has been advanced that unrestricted availability of genetic information could lead to the marginalization of young people of marrying age, particularly, women who are confirmed to be carriers of defective gene.

This last question touches on the difficult problem of who holds title to individual genetic information. The central issue in the cases given above boils down to who would be entitled to have access to such valuable information.

Patentability of genetic inventions

One issue which has raised serious questions is the supposed right to patent the technologies discovered in the process of gaining knowledge on the human genome and its medical applications. There is a worrisome tendency in some developed coun-

tries to apply to human beings the same principles as used for animals or plants. If so, we are once again faced with the grim reality of the scientific powers' absolute lack of solidarity with peoples who, due to resource limitations of different origins, are not in a position to invest sizable amounts of money in genetic research.

If were to come about such a situation would lead to a paradox in which some countries whose fabulous investments allow them to discover and apply deadly means for the nuclear destruction of human life are placed in the ethical predicament of not contributing to saving human lives by blocking access to the new technologies derived from the application of discoveries in genetics. In such a case, the business temptation to «recover the investment» could lead to serious setbacks for people living in the developing world. This should not be startling given the negative experiences witnessed by humanity, such as that of millions of human beings dying of hunger while economically powerful countries invest their money in the manufacture of sophisticated weapons –weapons, what is more, which are often deployed in those same countries to heighten international tensions and mutual mistrust between neighbouring peoples.

It is fitting to consider the opinions of Vicente, as recalled by Abrisqueta and Aller, when they affirm that «we are witness to a conflict between the ideas of the virginity and purity of science and the reality of its use in the service of economic and industrial interests». And they add that «the universality of the exchange of ideas and scientific discussions has thus given way to behaviour dictated by the secrecy which characterizes the corporate world» [25].

Nor can we forget that other experience, still with us, relating to the clamorous injustices of the terms of international economic exchange. Many are not moved by the situations I am describing here, but that, no doubt, is a problem of conscience, of human sensibility.

We must bear in mind that problems relative to the patenting of technological inventions and discoveries in the field of genetics are of pivotal importance for the future of humanity and the widening of the rift existing in the world today, in this area as well as in others, between countries with different degrees of development. In this respect, as is known, there exists the general

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[25] Abrisqueta, José Antonio and Aller, Vitalino: «Directrices éticas de la manipulación genética» [Ethica guidelines for genetic manipulation], *Fundamentación de la bioética y manipulación genética*, Universidad Pontifica Comilla, Madrid, 1988, p. 179.

principle of prohibiting the patenting of inventions relating to human beings. But agreement on this point does not prevent differences and disputes from arising when that principle is put into practice.

Opposed to the humanitarian approach of considering these inventions as part of humanity's common heritage, and consequently as exempt from any type of private appropriation, there has emerged an extremely vigorous campaign to maximally broaden the scope of such inventions' legal protection. There is a tendency to forget that biological techniques are different from all others insofar as they involve our biological existence. An obvious example of this protectionist tendency is the draft directive of the Council of the European Communities on the legal protection of biotechnological inventions».

The Human Genome Project's importance and the delicate ethical questions it poses have brought problems and criticism. The renunciation by Professor James D. Watson himself, for reasons known to all, is tied to these questions. As early as 1971 Watson was already warning of the ethical and legal dilemmas that would arise in the future –now almost the present– and urged that the ethical-legal consequences be carefully weighed or otherwise risk losing the possibility of freely deciding just solutions to the protection of human beings. Thus Nancy S. Wexler, involved in the Project, is right when she insightfully states that the mission of her group is «to anticipate now the abuses which could occur and prevent them before they happen». This is a rational and responsible attitude which should be shared by all in order to avoid foreseeable tragedies which humanity would once again have to lament after the fact.

Scope of support for the Human Genome Project

Nobody can question the freedom to pursue research and investigation within certain ethical parameters. Thus, it is reasonable to approve of support for the Human Genome Project, on the basis of the benefits it will produce, above all in medicine, and which can lead to enhanced human wellbeing. At the same time, however, the dangers of a misuse of the knowledge acquired by the Project are undeniable insofar as they could lead to acts contrary to the free and serene development of individual personality. Some of the risks might even mushroom into what could be classified as a catastrophe for the human race.

The great challenge now before the international community (this time fully aware of the problem) is to conduct a prior ethical

evaluation of the issue, to timely outline and approve ethical principles and legal provisions to govern the development of the Human Genome Project, and to protect the rights of all human beings to life, liberty and identity, and the other rights likely to be harmed by misapplication of genetic knowledge and techniques. It is only too reasonable to expect that we see no repeat of the uncontrolled use and generation of nuclear energy. We have only recently witnessed a war produced by such lack of control. There are no assurances that the country involved or some other country will not attempt or is not attempting to secretly (as per an old example) manufacture atomic weapons.

Perched on the threshold of the «discovery» of man's nature, approximately 100 years after Mendel, Mulligan was not being preposterous when he reflected that «given the power of present-day molecular biology, we may simply use gene transfer to make a cell do whatever we wish» and added «that within that cell we can play God» [26].

Meetings of the calibre and standing as the one which brings us here today will no doubt contribute to the search for a consensus on these serious and delicate matters for humanity's future, and help, on the basis thereof, form an international public opinion that can, without hindering freedom of investigation, control the misuse of biotechnology on the basis of agreements responsibly negotiated with due foresight.

The Human Genome Project and fundamental rights

Drawing on the philosophy of existence I have thus far discussed the scope of «freedom» in light of the latest reflections made with respect thereto. It is fitting to add that there exists, in my opinion, a basic trilogy of human rights or rights of the person which are essentially and structurally interconnected, as generally occurs with all personal rights. They are life, freedom –which sustains life– and identity. Identity means respect for each individual's personal «truth», that is, the acknowledgement that «each person is who he is and no other». Personal identity stems not only from one's unique genetic code, but also from the dynamics of the free development of one's personality according to an existential project or plan.

As is known, identity, which is always singular, embraces two facets. We refer to the static one and to the dynamic one. The

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[26] Reproduced from the magazine *Algo 2000*, Madrid, July-August 1990, p. 11.

first is made up of traits which are not altered or tend to remain unchanged, such as a person's fingerprints or name. The dynamic facet is made up of those traits which refer to personality, in itself and when it is projected socially. This is to say, it includes the cultural, ethical, religious, political, professional baggage and so on of each human being [27].

The crux of the problem confronting us, and which we must unravel with care, is to know the degree, measure and possibility with which the scientific and technical knowledge gained from the Human Genome Project might affect these fundamental personal rights.

Freedom and genetics

Freedom, within the context we have established in this study, is man's very «being». Man «is who he is»; he lives and develops only insofar as he is free. As Marcel stated «in the last instance, to say I am free is to say I am I» [28]. Or in Zubiri's words, «human existence itself is freedom» [29]. Freedom becomes the very sustenance of life and makes us identical to ourselves as temporal-historical beings. The integration of life, freedom and identity in existential union makes them reciprocally dependent and necessary.

While it is obvious and beyond all dispute that the findings and techniques derived produced by the Human Genome Project will impact many aspects of human personality –for instance, privacy– the extent to which they will influence man's root freedom may not be so clear to some.

Human freedom, as expressed earlier (see section 7), is not absolute but conditioned *inter alia* by our psychosomatic «casing», environment, upbringing, the behaviour of others, socioeconomic position, and cultural factors. Yet this is no impediment to affirming that man's very existence ultimately depends on the preservation of that freedom. It is therefore appropriate to repeat that only biological annihilation can definitively do away with freedom. However, all attacks on freedom of lesser order than this limit situation can to a greater or lesser extent hinder the freedom's phenomenological realization. Conditioned as it is by a wide variety of factors, freedom requires that the determinative power

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[27] Fernández Sessarego, Carlos: *Derecho a la identidad personal*, Ed. Astrea, Buenos Aires, 1992, pp. 99 and ff.
[28] Marcel, Gabriel: *El misterio del ser*, op cit, p. 296.
[29] Zubiri Xavier: *Naturaleza, Historia, Dios*, op cit, p. 388.

of those conditioning factors not be unduly magnified by science or the environment.

According to this outlook we must ask to what degree can the Human Genome Project's findings and technologies affect man's freedom, and thereby the free and serene unfolding of his personality, without endangering or fettering the realization of his existential projects. The first observation that comes to mind in the search for a coherent answer to this question is that freedom subsists in man for so long as he is alive. Only death produces the elimination of man's most inherent quality: his own existence as freedom. Freedom is always installed in man, though he is often not aware of this. Freedom may be intensely conditioned, but this does not impede its presence. As already pointed out, it avails itself of a set of elements to transform free decisions, concerning the subjective sphere of the subject, into free, phenomenal, objective actions; that is, to realize or to frustrate private decisions.

The various elements which condition freedom include human nature, the psychosomatic entity. Man relies, first of all, on his body and psyche to concretize his freely adopted decisions into inter-subject behaviour. It is in this biological realm that there come into play the most intimate determinants deriving from the subject's genetic structure. Any intervention on these elements, by diminishing or heightening the action of specific genetic determinants, will therefore ultimately impact freedom positively or negatively. The terrain for the free development of one's personality can thus be affected to some degree as a function of changes in genetic determinants.

Freedom and the Human Genome Project

According to the viewpoint outlined in the foregoing sections, freedom, understood as man's very being, could only be extinguished if the applications arising from the Human Genome Project directly or indirectly, proximately or remotely, were to cause the biological destruction of human beings or threaten with the disappearance or forced evolution of the human species. In these hypothetical situations, which could be considered as limit cases, it is obvious that such applications should be ethically condemned and prohibited outright. For life, and hence freedom and identity, are fundamental values safeguarded by law, which, in turn, is generally concordant with morals.

From another standpoint, to the extent that they can produce genetic variations, applications derived from the results of the Human Genome Project may work to increase or decrease the

weight of the biological constraints on freedom. If the psychosomatic entity is the first determinant to be reckoned with by humans when they adopt free decisions aimed at the fulfilment of a specific life project or particular conduct, then any change or alteration, for better or for worse, in the genetic sphere will affect the almost always narrow margin in which free decisions are made.

Scientists and moralists normally approve from an ethical standpoint of genetic intervention on somatic cells insofar as they do not affect the issue we are discussing here. Quite another case is that of genetic manipulation of germ cells, as it is from these cells that the existence and traits of a new human being are derived. It is this latter case which gives rise to the most disturbing questions, not only as to the unpredictable consequences for a specific human being, but also as regards the implications of such manipulations for future generations.

Genetic modification of specific human somatic cells is ethically and legally acceptable to the extent that it is designed to improve health and, thereby, enhance the factors which influence the quality of life. This will help place human beings in a stronger position to realize their freely decided plans; that is, to strengthen the action of freedom. This is positive for human beings.

Notwithstanding the assertion of the preceding paragraph, questions persist and concern heightens when considering the possible consequences of germ-line genetic manipulation. The justification generally advanced for such manipulation is a supposed «perfecting» of human beings of hitherto unfathomable consequences. This well-founded concern has led many writers to speak out in support of the «inviolability of the human genome» insofar as they regard these prospects, metaphorically speaking, as a journey into the unknown with consequences for future generations. Today's man would thus be determining the characteristics of future man.

Each human being possesses a biological structure which to some degree makes him more or less capable of realizing himself in a specific sector of vital activities. When vocation and skill coincide in a given individual very much can be expected of his creativity. It is desirable that genetic application, with appropriate ethical and legal controls, will at some point in their progressive technological evolution allow results beneficial to human wellbeing. This would serve to strengthen an individual's ability to realize his existential projects; that is, to attain through biotechnology larger arenas in which his free decision can be transformed, with as little genetic conditioning as possible, into phenomenal conduct.

The foregoing points to the conclusion that the Human Genome Project and its application can adversely affect freedom if, first, the limit case is reached in which the individual subject is extinguished because of manipulation of the evolution of the human species, or, second, if the biological determinants which condition each individual subject are reinforced. These negative prospects oblige us to carefully and with sufficient foresight weigh such possibilities in order to determine their effect on human liberty, and to adopt appropriate measures for preventing their realization when they entail harm or the risk of harm.

Systematic study of the negative effects of somatic genetic applications that could constrain and, in some cases, impede freedom, might at the same time spur negotiation and subscriptions of international conventions. If they sidestep the errors committed in the case of atomic energy, such agreements could lead to an international ethical-legal regulation of the genetic manipulations ushered in by the Human Genome Project and its findings.

It would be to state the obvious to repeat that such regulation should be guided by the principle that genetic interventions and the biotechnology resulting from development of the Human Genome Project must be placed in the service of humanity and aim to improve the quality of human life.

The life of freedom and the human genome

Appeals to freedom inexorably lead us to the values of life and identity. There is no life or identity without freedom; nor, obviously, freedom or identity without life. Essentially intertwined, they are mutually interdependent and are in dynamic interaction. This root connection, which is given in the unity of the human being, implies that any alteration in one will eloquently and immediately impact the others, although the effect will vary in each instance according to the magnitude and nature of the alteration.

Life is sustained by freedom, for the former would be impossible without the permanent action of the latter. There is no life without projects or plans that suppose free, personal and evaluative decisions. One cannot make plans without living or live without planning. Similarly, freedom, on its phenomenological realization projects the dynamic identity which the subject has been fashioning through the chain of free decisions within and despite the genetic and environmental determinants framing him.

A human life has richer possibilities when its genetic and environmental determinants do not overly constrain or limit its freedom.

The relative overcoming of certain determinants, be they genetic or environmental, to a certain extent and in certain actions facilitates the freer development of the individual's personality. The inalienable intimate instance of liberty, which is pure subjective decision, thus acquires broader spheres for its free action and, thereby, for more effective fulfilment of existential projects.

Conversely, any unfavourable genetic intervention affecting freedom impoverishes the quality of life of the person by impairing his possibilities for personal self-realization. When a genetic manipulation places any kind of constraint on a person's freedom, it is life itself which is directly affected.

Freedom, identity and the human genome

A human being is entitled to respect for his identity, which, in turn is a product of his liberty, of the realization of the existential projects which shape his personality. Each person therefore has the right to be recognized as «himself and no other»; that is, the right to protection not just of his static identity but also of the dynamic identity he socially projects.

To negate, dispute or alter someone's identity –static or dynamic, for they are one and the same– is to intervene negatively in the free decisions of that person. Given man's ontological structure, any modification of a person's identity has repercussions for his freedom. The tight, essential connection between freedom, life and identity requires their simultaneous joint legal protection. And jurists seem to have recently come to this understanding. This perception is becoming more consolidated as some of the mysteries of the humankind are unravelled, irrespective of whether the discoveries are quarried from science or philosophy. Man's sensitive structure involves the interaction between all his potentialities and attributes. And it is in this essential connection where one of the greatest dangers of thoughtless, hasty or audacious genetic manipulation any intervention can be found.

The idea succinctly expounded in the preceding paragraph allows us to conclude that any action affecting a human being's freedom will inexorably impact on the quality of his life and on his very identity. And this is of utmost importance with respect to protecting freedom from any genetic intervention tending to limit or restrict it by intensifying its determinants or creating new or heavier constraints. Genetic interventions which undermine freedom thus have multiple and transcendental consequences for the individual human being.

It is important to attain the greatest ethical and conceptual clarity possible in order to grasp, day by day, the ethically and legally permissible limits as to genetic interventions. It is not a matter of obtaining a «new» man different than what «he himself is», but a better somatically endowed human being. This will no doubt be achieved to the extent that we manage to overcome or limit the negative impact of genetic diseases that condition or impede the free and full development of human beings.

Science must respect the freedom of man «to be himself» and not attempt to modify or alter his natural characteristics, under the false argument of «perfecting» him, so as to affect his identity and, thereby, his freedom. It is not a question of envisioning a «different» man, but rather a somatically «better» man, without altering his identity; that is, without modifying the set of characteristics, skills and attributes that make up his freely forged personality. Hence, genetic optimization of personality should not be allowed insofar as it harms the identity and, therefore, the freedom of the person to be «identical to himself and to no other».

Human beings have the right not to be «programmed», as that would be tantamount to yielding a person's decision-making function to some external centre of power, that is, to relinquishing one's inalienable personal freedom, the same freedom which makes each human being «himself and no other». Human beings should be legally empowered to block genetic interventions which clash with ethical precepts and undermine the identity that each individual has freely forged and projected. It is with their own identity, and not that imposed on them by others, that they wish to be recognized and live out their lives.

The relativity of rights

The potential of genetics, which has been described as apocalyptic, endangers the life, liberty and identity of human beings. Moreover, the evolution of the human species is at stake. These are truths which can be neither ignored nor denied. Too great is the power assumed therein by man, and too dangerous the temptation to wield it irrationally, as has occurred in the past. Hence the cogency of the prominent voices calling for maximum caution and utmost circumspection in how biotechnology should be handled.

Rights are not absolute. This principle, grounded in the coexistentiality of man, shows us that every right entails a duty. Each right is accompanied by a duty at two levels, the generic and the specific. The first implies that the duty to respect the rights of

others is also operative in the exercise of every right. In addition to this general duty, which is inherent to all subjective rights, there is a specific duty that stems from the nature of the particular right in question.

The right to free scientific investigation does not escape this rule. Like all other rights, it is not unlimited. Every investigator is, in the exercise of his right, necessarily subject to the generic duty to respect the overall social interest. The right to free investigation is restricted by the duty to not violate public safety, the freedom of every human being, their lives, their identity, their private realm, their serenity. None of these rights can be left to the discretion of the investigator, however responsible he may be, or subject to private control. The nature of the specific right to genetic investigation is of such importance to human life that it requires international public control.

Civil society has the right to protect itself from any abuse or deviation in the research and investigation process. A well-structured international legislation would judiciously balance society's interest in making maximum use of the beneficial aspect of investigation with a adequate public control for avoiding harmful excesses in the application of biotechnologies.

The difficulties entailed in achieving the above objective cannot be ignored. Many powerful interests are involved, and power, in any of its manifestations, can wield immense charms for human beings. Nonetheless, we have the duty to not relent if we truly value human freedom and the intrinsic dignity of humankind.

MAN'S FREEDOM AND THE HUMAN GENOME: GENETIC KNOWLEDGE AND THE LEGAL SYSTEM

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There are at least two ways to describe the relationship between genetics and the law. In the first instance, genetic research and technology represent powerful forces for change. The law, meanwhile, is a mechanism for maintaining stability. When the two forces interact, there can be considerable tension, as the introduction of new genetic knowledge brings the law face to face with what may be unprecedented situations. In the second instance, however, the law embraces genetic research and technology as effective tools for enhancing its institutional functions. For example, DNA typing may increase the power and ability of the State to enforce its laws. And the ability to identify people genetically vulnerable or predisposed to some type of illness or behavior may present the legal system with new mandates or opportunities for social control, all in the name of maintaining a stable social order.

The power and potential of genetics lies in the knowledge it provides. And the information gained from that knowledge will be of great interest to individuals as well as to others –family, employer, school, insurer, and the legal system. But such knowledge is a double-edged sword, in that it may restrict or expand human freedom by the choices it offers. For example, knowledge

of one's susceptibility to a genetic disorder opens up the possibility of prevention or treatment that was not a consideration when ignorance or uncertainty prevailed. There are now more opportunities to alter life's course. Even if nothing can be done to avoid the ill effects of the disorder, people will be able to make more informed decisions about their lives and their relationships with others.

There is the possibility, however, that people informed of their genetic predisposition to disease, even if the risk is slight, may equate heredity with inevitability and destiny, and believe that life offers them few real choices. And other people and institutions, believing the same, may treat them in a way that also restricts the way they live their lives. It is also quite possible that genetic knowledge will provide a reasonably objective basis for classifying people with respect to characteristics and capabilities. Such classifications may create access to entitlements that open up new opportunities and choices. At the same time, however, they may also subject persons to new forms of discrimination, stigmatization, and control (Dreyfuss and Nelkin 1992).

Genetics and the legal system

I will focus my remarks on the implications for human freedom of the use of genetic knowledge in the legal system, specifically as it applies to criminal responsibility. Throughout the world, the law uses scientific expertise to evaluate the extent to which an individual should be held responsible for antisocial behavior and to assess that individual's potential for rehabilitation. These evaluations affect decisions about culpability and punishment. The possibility that genetic-based knowledge will contribute «hard» evidence about these matters is clearly an attractive proposition for the legal system.

Definitive evidence linking genetics and behavior could contribute to a more speedy and less costly resolution of cases by replacing the often conflicting, drawn-out partisan «battle of the experts» that tends to overemphasize divergence in scientific opinion at the expense of areas of agreement. A predictive capability of genetic knowledge would also permit a more rational allocation of resources with respect to decisions regarding incarceration, treatment, and/or rehabilitation. As our understanding of the genetic bases for behavior improves, it is likely that there will be an increased demand for and greater acceptance of genetic evidence by the law. But we must be alert to the danger of according too much authority to genetic knowledge in the legal system. It is neither infallible nor determinative in many cases. Such knowledge should not routinely be allowed to trump other relevant

factors, such as the environmental elements that influence the behavioral expression of a genetic condition.

Genetics, behavior and criminal responsibility

The increased use of genetic knowledge in the legal system promises to do more than introduce hard evidence into the adjudication process. It will also influence how we define criminal responsibility and how we believe the legal system should respond to criminal behavior.

When we say that someone is «responsible» for his actions, we mean that the action was taken *knowingly* and *willingly*. Since there are degrees of knowledge and intent, there are also degrees of responsibility. Traditionally, Western societies have considered responsibility mitigated by conditions which diminish the knowledge available regarding the possible consequences of one's actions. It may also be mitigated by limits on one's freedom to choose. Among such limits are the lack of control over one's behavior because of constraints imposed by others or by behavioral impairment.

To the extent that one's genetic endowment predisposes an individual to antisocial behavior, it may be difficult to hold him fully responsible for his actions. A genetic predisposition to criminality might also influence the kinds of sanctions imposed (Morris 1994). What kinds of influence it should have is subject to some intriguing speculation. The norm has traditionally been that the «punishment should fit the crime», that is, that the severity of the punishment should be directly related to the seriousness of the harm caused by the criminal behavior. But what if a genetic predisposition indicates a strong tendency toward future dangerousness? Can the State, not in the name of crime but for social protection or the provision of treatment, impose harsher sanctions than might be warranted by the nature of the crime? The limits of the predictive value of genetic knowledge should caution against proceeding quickly to impose a punishment that exceeds the severity of the harm.

Some cautionary observations on the use of science in the legal system

What is so attractive about science to the legal system is its apparent objectivity, predictability and certainty. But what is projected in appearance is often elusive in reality.

1. Objectivity

The aura of objective truth associated with science in the popular mind makes it very appealing to a legal system in search of hard evidence to validate its institutional role and to support its claims of fairness when imposing restrictions on individual freedom. But like all human endeavors, science is socially situated, affected at every stage by personal, professional, and social values. «Facts are not pure and unsullied bits of information; culture also influences what we see and how we see it» (Gould 1981, pp. 21-22). Science is not value-free, and even facts are subject to interpretation. This is not, of course, reason for the legal system to reject the findings of genetics research, but it does require critical evaluation to determine which interpretation generates the most reliable and valid «factual» claims.

2. Predictability

Genetic researchers anticipate that science will increasingly develop tests that will indicate predisposition to a wide range of genetic anomalies, including susceptibility to behavior disorders (Holtzman 1989). Such a predictive capability is very appealing to the legal system, which has as one of its functions protecting society against possible criminal behavior. But the actual predictive value of such tests is limited by our gap in knowledge about the precise relationship between predisposition and actual expression of the genetic-based behavior. Treating all people at-risk for a particular behavioral disorder in the same way, without knowing who among them will eventually manifest the disorder, is prejudicial, and unlikely to be cost-effective. To say that a person is at-risk genetically is only part of the human equation.

3. Certainty

For the legal system, science also promises to introduce a level of precision into a process often steeped in ambiguity. Certainty increases efficiency and validates outcomes. But science is far from a precise endeavor, and scientists are cautious in embracing new findings or theories that run counter to accepted doctrine. Even within the field of genetics, the nature/nurture dispute is evidence that scientists themselves are far from certain about where knowledge of genetics is leading.

Conclusion

Beyond these three concerns are more fundamental questions of how genetic knowledge should be used in the legal system and

whether genetic-based behavioral disorders should be treated as an illness or punishable as a crime. In dealing with the former question, one must consider some fundamental differences in the way science and the legal system perform their functions. In science, knowledge is acquired by repeated observations and experiments, and what is known can change over time. In the legal system, however, decisions must be made at a particular point in time, and cannot typically wait while science continues to revise and refine its work. Given these different approaches to determining the «facts», how can the law make the best use of the knowledge generated by science? There might be much to learn regarding the use of genetic knowledge by examining how science generally has been applied to the resolution of legal issues (Carnegie Commission 1993). The other issue –whether to treat genetic-linked behavioral disorders as an illness or crime– presents a more fundamental normative challenge. It raises questions about the meaning of such concepts as justice, autonomy, responsibility and culpability, all of which are intimately linked to human freedom. Genetic knowledge creates choices for both individuals and social institutions, and not infrequently, those choices come into conflict. How that conflict is resolved with regard to the law will have profound consequences for the treatment of persons by the legal system. Underlying all of this is a challenge to researchers and clinicians to consider their responsibilities and capabilities for preventing improper interpretations and applications of behavioral genetic knowledge by the law.

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CLAIMS AND EVIDENCE

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Claims that the identification and sequencing of all human genes (as a result of the Human Genome Project) will give us the key to a wide range of disorders have been made by scientists and non-scientists alike. Daniel Koshland, a distinguished biochemist, and the editor of *Science*, has «argued that no group would benefit more (from identifying human genes) than the homeless, since many of them suffer from disorders that would eventually be prevented or treated thanks to the genome project» [1]. A story appeared on the front-page of the *New York Times* last year under the headline «Studies find a family link to criminality» [2]. A recent news report in *Science* suggested that divorce might have a genetic origin [3].

Do genes contribute substantially to homelessness, criminality, divorce, and other complex problems such as alcoholism and learning disabilities? If so, will finding the respective genes solve

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[1] Powledge T., *Toward the year 2005*. 1989, 246 (8); Supplement: pp. 1, 6-7.
[2] Butterfield, F., «Studies find a family link to criminality». *New York Times*, 1992 January 31: 1.
[3] Holden C., «Why divorce runs in families». *Science* 1992, 258: 1734.

these problems? The publicity given to genetics suggests an affirmative answer to both questions. If the claims were true, then knowledge of the human genome would pose a threat to man's (and woman's) freedom. Before discussing that threat, I will consider the science and the evidence behind the claims.

The identification of human genes will improve our ability to detect, and in some cases treat, disorders that are inherited in accordance with Mendel's laws and can, therefore, be explained by mutations in a single gene. The mapping of disease-related genes depends on finding families in which a trait or disorder follows Mendel's laws. Claims that genes had been found for bipolar affective disorder and schizophrenia –two disorders that Koshland may have had in mind in his comments on homelessness– were based on studies in families in which the disorders appeared to follow Mendel's laws. Additional study of these families has led to retraction of the early claims [4]. Moreover, only a minority of homeless people have mental illnesses [5].

Occasionally, a small proportion of people with a common, complex disease will be observed to have inherited the disease in accord with Mendel's laws, strongly suggesting that the disease is of single-gene origin *in these families*. This has been proven for a small proportion of patients with hypercholesterolemic coronary artery disease, Alzheimer disease, and colon and breast cancers, and may yet prove to be the case for bipolar affective disorder and schizophrenia. Because Mendel's rules are not followed in the majority of families with such diseases, we know that more than alterations in a single gene are needed for the disease to occur.

The gene in which mutations account for a single-gene form of a disease could be entirely normal in complex forms. Alternatively, the same mutation (or mutations) could be present, but its effects modified by the presence of variant forms of other genes, or by life styles, diets, and/or environmental exposures. Or, different mutations could be present in the same gene, but ones that do not cause such a severe effect except, again, in the presence of other genetic, behavioral, and environmental factors. Only when most if not all of these other factors are elucidated, and methods developed to determine their presence, will it be possible to predict the future occurrence of complex disorders with high probability.

Unfortunately, the mathematical techniques used to map genes in which mutations lead to Mendelian diseases will not suffice to locate genes that contribute to, but are neither necessary nor sufficient

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[4] Horgan J., «Eugenics revisited». *Scientific American* 1993, 268 (6): 123-31.
[5] Winkleby M, Rockhill BJD, Fortmann, S., «The medical origins of homelessness». *American Journal of Public Health* 1992, 82 (10): 1394-8.

for, the occurrence of complex, multifactorial diseases [6]. Another method involves looking for an association between a variant form of a «candidate» gene, which could plausibly explain occurrence, and the disorder. Claims that this approach led to the discovery of a gene for alcoholism have not been substantiated [7]. Other approaches, such as twin and adoption studies are fraught with difficulties [8], and cannot lead to identification of specific genes.

It is highly doubtful, therefore, that mapping the genome will give us tests of high predictive value for complex disorders. Only when we are capable of detecting all of the multiple factors that account for a disorder will that point be reached. For nebulous «disorders» like homelessness or alcohol abuse the most important of these factors may be the social milieu. The individual at risk may be powerless to do much about it.

If genes do not contribute substantially to homelessness, criminality, and other complex problems, genetic research is unlikely to result in solutions to these problems. Why then are exaggerated claims made? It is easier to forgive reporters, who may not know better, for making them than scientists, who should have some familiarity with genetics. Perhaps, they make them to promote genetic research. In the United States, funding for the Human Genome Project requires the assent of the Congress. Few Congressmen have heard of many rare, single gene disorders, but they have heard of the common diseases and are more likely to give their support to research that deals with them. Unfortunately, claims that cannot be substantiated may lead to a backlash against support for scientific research. Claims for the benefits of genetic research may fan fears of eugenics or, as the title to this Section suggests, pose threats to man's freedom.

There is, I believe, another reason for these claims, and it also threaten's the freedom and dignity of men and women. It is the simplistic attempt to attribute complex problems to single causes in this case, genes. This can be viewed as a form of victim blaming, but one for which the victim –who cannot choose his or her genes– is blameless. The genetic solution absolves society of its responsibility for complex problems. The frequencies of homelessness, alcoholism, criminal behavior, and divorce differ between countries and over time in the same country, suggesting that genes do not play a major role. Freedom would be better served by looking for the roots of complex problems in more fertile soil than the human genome.

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[6] Greenberg D., «Linkage analysis of "necessary" disease loci versus "susceptibility" Loci». *American Journal of Human Genetics* 1993, 52: 135-43.

[7] Gelernter J., Goldman, DRN., «The A1 allele at the D2 dopamine receptor gene and alcoholism». *Journal of the American Medical Association* 1993, 269: 1673-7.

[8] Horgan H., *Opus. Cit.*

MAN'S FREEDOM AND THE HUMAN GENOME

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On Thursday last, in faraway Sydney, Australia, I was dressed in crimson robes. I was confirming or upholding appeals from people who are in prison at this moment, because of decisions by me. On Friday last I was sitting in civil appeals. My first legitimacy to speak to you is because I am a judge. At the bottom line, at least in the common law system, which the English speaking people have followed, the decisions in relation to genetics, in relation to the Human Genome Project, for default of any other law, will be decided by people like me. Judges will have to fill any gaps us the law. Self-evidently, this is a pretty defective system. But it is the result of failing to act efficiently to developed well thought out and principled law. How could that be done? At the national level, the resistance results from the fact that the politicians in Parliament find that the problems of the kind presented by the Human Genome Project, are very daunting. No votes in them. Perhaps votes to be lost in them. Nothing tends to be done.

In Australia, I chaired the Law Reform Commission for 10 years. It helps the Federal Parliament in developing the law. Justice Jean-Louis Boudouin did the same thing, in Canada. The Australia Commission, early in its life, was asked to look at the law on human tissue transplants. That task presented a very crude, but somewhat analogous problem to the problem we are dealing with here. The Commission got together the experts. We consulted

the community. We consulted the people who were most involved, as Frits Hondius said we should. We ultimately produced a report which faced up to the hard questions; the definition of death; do you allow infants to donate organs; do you adopt opting in or opting out; do you permit the sale of body parts? Problems of the kind which are being presented in the Human Genome Project in much greater multiplicity and complexity.

On the international level, because this is an international problem, we have an even greater problem. At that level there is a diversity of cultures, religions and legal traditions. But things can be done. In an earlier manifestation of the impact of technology on the law, I chaired a committee of the OECD looking at the development of guidelines for trans-border data flows and the protection of privacy. Those guidelines were adopted by the OECD. They were accepted by the OECD, recommended to the member countries. Now, almost every member country, including my own, including Japan and New Zealand, countries with utterly different legal traditions, have adopted legislation, binding and enforceable in their countries, for the protection of privacy in the context of trans-border data flows. These laws are based upon, or at least greatly influenced by, the OECD guidelines. It gets a little irritating, to a person from Australia, to sit and listen to what is being done in Europe. Or to sit and listen to what is being done in the United States. The Human Genome Project, like informatics, is a *global* concern. It is not simply a concern to Europe or North America. It is of concern to all humanity: perhaps much more acutely so than informatics. So we have to develop global institutions to deal with this issue. It can be done. In The Global Commission on AIDS, for example, principles are being developed for how to deal with prisoners who have HIV AIDS. Those principles, formalised in Geneva, are being reflected in local policy and legislation. So with all due respect to HUGO, I think we have to get something with the legitimacy of governments behind it, which can give the impetus, in a trans-continental way, to the problems of the kind we have been hearing about today and about which we will hear more tomorrow.

There are other matters which should concern us. We have heard of some this morning. The concern of government attitudes. When Karl Brandt, one of the Nazi doctors, went to his death, he said, «I only did what I did for my country in a time of war». And that was the suggested justification for him for breaching the basic principles of international humanitarian law in relation to scientific experimentation. We may dismiss that. The Nuremburg Code may say that Dr Brandts excuse was not good enough. But in the recent Operation Desert Storm in Iraq, the United States government excepted its soldiers, and other operational personnel, from the principle of informed consent. It did

so because it said this was necessary for to the defence of the national interests of the United States.

So when we look at the problems ahead of us, we have lessons to learn from what has gone before. And we also have lessons to learn from this meeting. Most of us comfortably off people from the occidental tradition. Almost all of us. This is a problem which concerns, as we have heard, the Japanese. If the South Koreans and the Singaporeans and the Chinese are not there in scientific developments in great numbers now, they soon will be. Most of them do not share all of our fundamentals. The Confucian renaissance which we face in the world starts from utterly different premises: Not the individual but the community. Not rights but duties. Not the rule of law, but the rule of powerful men of virtue. So I am very glad when I hear that scientists are coming together to talk about the Human Genome Project. But I will be gladder still if we could get together lawyers and ethicists with the scientists. I would be most glad if there were lots of oriental faces about, and black faces about, to deal with issues which are common to all humanity.

As I came here, and no-one came to this conference from further, I thought about the great social experiments of our century. There was Prohibition, and it failed. Yet we still bear the scars of it on an international level in our response to drugs. There was communism, and it failed. There is self-determination of peoples. The principles of self-determination are still working their way out. Today, ladies and gentlemen, was Empire Day. This is Queen Victoria's birthday. When I was a boy in Australia, we celebrated it as a symbol of the Empire upon which the sun would never set. Well the sun did set. The self-determination of peoples works its powerful messages in Yugoslavia and in the Soviet Union.

The other great experiment was eugenics. We have to learn from history, lest we repeat its mistakes.

I have five commands with which I'll finish this session. I would have 10, like the Almighty, but the Chairman has not given me time enough. Perhaps the Almighty should have been similarly limited. He might have left one or two of them off is list.

The first is, that not to act, not to make legal principles to deal with the problems presented by the Human Genoma Project, is to make a decision. Science will then rush ahead and it will not be controlled in a way in which perhaps, in retrospect, we as human beings, would want. Secondly, we should seek to frame our laws on the subject consistently with international human rights law. In these two points I reflect what Frits Hondius has

said to this workshop. Thirdly, and Frits Hondius said this too. We have to consult not only the general community, but we have to consult all involved. All people who are actually or potentially going to receive the benefits and suffer the problems of the Human Genome Project should have a chance to be heard. Fourthly, as in AIDS, we must base our laws and policies on good science, not on ignorance or mythology or even, with respect, religion. But on good science. And fifthly, in order to be effective, we have to find global mechanisms.

In a way, the last command presents the greatest challenge of all. However, it can be done. For the sake of the Human Genome Project and for the sake of humanity, it should be done. We, who meet here in Bilbao, must play a part to make sure that more is done and that there is a great sense of urgency in providing society's response to this great scientific advance.

BENEFITS AND LIMITS OF FREEDOM IN GENETIC SCIENCE

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Non-freedom in human society

The concept of freedom has a hundred faces. Some of the faces show the characteristics of genetic science and technology. Through their eyes are seen, for the first time in history, the infinitely small components of the cell and the DNA molecule. By their ears are heard the cries and moans of countless persons who suffer the distress and pain of congenital diseases and the pangs of hunger. By their mouths, the faces of genetics speak a new language of contigs and RiFLiPs and polymorphisms, but also the language of food supply, disease prevention, therapy and health. These are words of hope and cheer for persons who are politically and economically free to enjoy the promised benefits. However, for the large proportion of humanity for whom such freedoms have no reality or meaning, much of our enthusiasm for the Human Genome Project and most of our debates about ethical, social and legal issues make no sense. We know that genetic research is highly important and the discussions indispensable. Nevertheless, a serious concern for human freedom must keep us sensitive to the moral imperative of extending freedoms of disease prevention to all

who remain in bondage to diseases, disabilities, poverty and hunger.

Freedom to know

Some faces of freedom express opportunity and openness both to know and to do. This is freedom to learn and freedom to apply what is learned. In addition, the word «freedom» means emancipation and liberation from powers and conditions of restraint or captivity.

In the sphere of molecular biology and genetic engineering, the freedoms to know and to do are unambiguous, self-evident goods, according to the belief of many people. In the language of human rights, as encoded in the several declarations of the United Nations and expressed in the constitutions of democratic nations, the freedom of inquiring, thinking and learning is an unconditional good. It is virtually a natural law, which no intelligent, right-thinking person would question or violate. This freedom belongs to the charter of modern science. True enough.

Can we assert, therefore, that there are no inhibitions or restraints which may justly be imposed on the freedom to know? In theory, at least, we affirm an unconditional freedom of inquiry and research. But in actuality, we have to recognize that there are limits to this freedom. Some limitations are acknowledged as a matter of prudence and personal judgment; others are imposed by powers which are either related to the researcher's institution or are rather remote from it. Some examples come to mind which are of varying degrees of gravity of importance. Here we confine our thought to actual or recommended restrains upon the freedom to know. Then we will consider those which affect activity.

There are few places in the world where *laissez-faire* applies without qualification to market economies. Likewise, the field of genetic research is not without boundaries of learning.

Question: Can predisposition toward violent and criminal behavior be due to genetic causation? Answer, as given by the director of the National Institutes of Health in the US: This is not a legitimate question. So funding for a research project, costing $78,000, was cancelled soon after the grant had been awarded and plans for a conference had been made. Was this retraction a flagrant violation of academic, intellectual freedom? Yes, said medical geneticist Paul Billings of San Francisco. No, said Ruth Hubbard and Elijah Wald of Cambridge, because the inquiry is

inevitably biased on favor of those who advocate eugenics or believe that «racial inferiority» and «criminal disposition» are corollaries and are genetically based [1]. At issue is not the question itself, but the freedom to discuss it, and eventually to reveal the scientific and social evidence for accepting or rejecting the matter.

Discovering the gender of an embryo has become almost commonplace as a procedure in pre-natal care. Is there not a freedom to know whether a male or a female baby is either to be expected –or perhaps destroyed? This issue is much more complex than one of intellectual inquiry. Such knowledge is too dangerous to learn, say some; it should not be allowed even to be sought. A prohibition derived from moral and religious opposition to abortion is consistent with this view.

Eastern Orthodox, Roman Catholic and certain Protestant churches affirm that restraint on freedom of knowledge. They believe that the value of maintaining a human life transcends the value of knowledge and free inquiry. Yet, other churches which are permissive on abortion also join in a «call for the prohibition of genetic testing for sex selections» [2]. There is moral ambiguity here for vigorous proponents of feminism, due to the long established cultural tradition of favoring male children over female. In India and China, where population pressures are clearly dangerous, abortion and even infanticide of females is common. Even apart from such cultural patterns and religious rules, however, there is opposition to determining embryonic or fetal gender. In their widely cited study of genetic practices in twelve nations, John C. Fletcher and Dorothy C. Wertz found disagreements on whether testing results should be kept in full confidence by the physicians. The researchers came to their own conclusion that «diagnosis should be used only to give parents and physicians information about the health of the fetus» [3], with the one exception of sex-linked diseases like Fragile-X, where confidentiality would be unethical. They advise, in effect, that parents have no right to know; but they affirm the general right of 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 female is violated, and 3) sex selection is a precedent for eugenics... Sex selection discredits the public image of prenatal diagnosis and of medical genetics» [4].

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[1] Billing, Paul; Hubbard, Ruth and Wald, Elijah, 1992 (November). «Academic freedom; responsible science». *Gene Watch*, 8: 1-3.

[2] World Council of Churches, 1989. *Biotechnology: Its Challenge to the Churches and the World.* Geneva. World Council of Churches, 2.

[3] Fletcher, John C. and Wertz, Dorothy C., 1990. «Ethics, law, and medical genetics: after the human genome is mapped». *Emory Law Journal*, 39:789.

[4] *Ibid.*, 788.

Their ethical reasoning is thus based equally on principle and pragmatism, not explicitly on religion.

The religious impulses of member churches of the World Council of Churches impel them to advise «governments to prohibit embryo research with any experiments, if agreed, only under well defined conditions» [5]. Whatever those conditions may be which are «well defined» are not defined in this resolution! Yet the churches seem reluctant to be so categorical as the Roman Catholic instruction of 1987, which allows no interventions for experimental purposes but only for therapy of the fetus [6]. The latter condition is presently met by fetal surgery *in* or *ex utero,* which has been practiced. But gene surgery at the zygote stage –following *in vitro* fertilization and preceding uterine implantation– is excluded. Preimplantation selection of zygote cells, while still plenipotent for individual development, is illicit in the Church's view, however much useful information it might yield [7].

So much for exceptions to freedom of genetic research. Another aspect of this freedom needs to be mentioned with emphasis, however. The counterpart of freedom in moral terms is always and everywhere responsibility. In the fields of scientific research, notably in genetics, there is no knowledge for simply its own sake. De-coding DNA and learning the secrets of recombination and the creation of proteins is not an intellectual game like a crossword puzzle for pleasure or chess for competition. Genetic research requires communication by the sharing of information of discovery. This is why journals exist in great numbers, the papers of which are indispensable.

A non-scientist can offer a most respectful suggestion. It is this: let genetic researchers recognize their responsibility not only to colleagues within their sub-specialties, but to the wider human society of which they are indispensable members. Some, to be sure, are able to move easily from bench to lecture hall, television, word processor and conference room without detracting from their primary research. They are outstanding, but few in number. The great majority consists of those who pursue their research in a narrowly delineated area without participating in any inter-disciplinary discussions of the wider implications of their efforts. The American program of Ethical, Legal and Social Issues (ELSI) within the HGP is achieving this purpose through broadly representative conferences and study projects. Yet, it would bet-

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[5] World Council of Churches, *op. cit.*, 2.

[6] John Paul II, 1987. «Instruction on respect for human life in its origin and on the dignity of procreation». *Origins,* 16: 697-711.

[7] Grobstein, Kenneth, 1988. *Science and the Unborn,* New York: Basic Books, 1988. He recognizes the inhibitions against experimentation, but deplores the unavailability of much valuable embryological information because of them.

ter serve the interests of all persons concerned with, or affected by, the HGP if small, informal ELSI discussions were taking place in all localities where the researchers are at work. Universities and major medical centers are the naturally favored locales. Some biotechnology firms, notably Genentech, are now urging their researchers to engage in the wider conversation.

Freedom to act

Two popular clichés cause misconceptions about genetic science. One is the idea of «playing God». The other is the notion, «what can be done ought to be done». Uncritical repetition of them has already caused much confusion of understanding. The frequent use of «playing God» is frivolous because it posits a God who uses omnipotence in a capricious manner without moral direction or restraint: a cosmic magician whose work of creation of matter and life can now be emulated by geneticists. The mythological Zeus may fit this picture, but not the God of Jewish and Christian faith, at least. The fallacy of «doing everything that can be done» ought to be transparently evident also. As a maxim it serves no practical purpose. It disregards both moral and economic constraints. Science-based technology makes possible all sorts of works which pollute and destroy the Earth's environment and those which wreak havoc on humans, whether by intention or inadvertence. Moreover, «what can be done» has to be subject to economic realities of usable resources for the most needed purposes of benefit to humanity. Nevertheless, these clichés continue to distort the public discussion of freedom to act upon genetic knowledge and resources. There is no inevitable line between the freedom to know and the freedom to do.

The key words in debates over the limits of genetic engineering are «choice» and «dilemma». The question first raised about a feasible but dubious project is «who decides»? When the positive and negative factors seem to be evenly balanced, it is conventional to speak of «ethical dilemmas». During the past 25 years, two policies have developed which are generally honored in practice. One is the rule of «informed consent», initiated by the World Medical Association. Its counterpart' in America are the Institutional Review Boards, which in many communities evaluate and judge research protocols with respect to the use of human subjects in experimental procedures. More recently, to these kinds of regulation have been added very strict rules for the humane treatment of animals, mice to chimpanzees, in experiments. The freedom to engage actively in biological sciences and medicine, then, is much more subject to limiting constraints than the free-

dom to know. Some examples may be described, both those in current effect and those recommended.

The Recombinant DNA Advisory Committee of the NIH was born in 1975, when microbiologists were very apprehensive over potentially dangerous consequences of the new technique. The famous conference at Asilomar, California, was lauded as an unprecedented instance of how scientists could impose restraint –indeed, a moratorium– upon their freedom to act. The committee has demonstrated ever since then a remarkably thorough ability to withhold approval of somatic gene therapy on human patients until the last barriers to a safe and harmless outcome have been surmounted. This was true in the 1990 case of Dr W. French Anderson's successful gene replacement therapy for a child with the very rare disease, adenosine adeaminase (ADA) deficiency. This cautionary preparation which lasted several years, has opened the way to other procedures for treating patients with genetic diseases.

By contrast, the access to germ-line, or sex cell, therapy remains closed, so far as governmentally funded research is concerned. In this case, there are at least three main hindrances. One is the technical problem itself, which is much more complicated that treatment for a single gene deficiency. The second concern is due to the acknowledged fact that altered germ-line cells are irreversibly changed for all subsequent progeny. This means that the risk factor remains unknown and formidable for individuals yet to be conceived [8]. The third hindrance is philosophically moral and theological. It is a fear that arises not only from risk but also from anxiety over possibly doing irreparable violence to human nature. Successes in germ-line therapy would encourage efforts to change human genotypes and phenotypes by so-called enhancement of characteristics and abilities.

Opposition to germ-line manipulation for these three reasons has been expressed by religious bodies for 10 years. Both the National Council of Churches in the USA, 1986, and the World Council of Churches, 1989, took strong positions: strong but not absolute. The former recommended an approach «with extreme caution». And the latter, addressing a world-wide constituency, urged a ban on the effort «at the present time». This is ostensibly because we cannot know in advance what new procedures might be invented which would remove the fear of undue risk to future individuals, and eventually to the human gene pool.

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[8] Nichols, Eve K., 1988. *Human Gene Therapy.* Cambridge: Harvard University Press, 165.

The freedom to research in genetics is restricted in various countries by different kinds of regulatory policy and law. Justification for limiting freedoms is generally explained as protection of persons, animals and environment. The protection of commercial enterprises is also a major consideration, especially in the United States. Many scientists advocate maximum freedom of research, although they concede reluctantly to the inevitability of some controls. They want to enjoy freedom of access to all kinds of living organisms found in natural state as well as those modified by genetic interventions in the forms of genetic fragments, bacteria, worms, fish and mammals. The rationale for this freedom rests primarily upon the givenness in nature of millions of species. As some express it, these organisms are «the earth's commons». Individual specimens may be owned, of course, but not whole species or sub-species, it is claimed. Nevertheless, that concept of ownership has been radically revised by the US Patent Office. In much disputed decisions, patents were awarded on bacteria in 1980 and on mice in 1988. Since then the numbers of patents on transgenic animals have grown with the rapidly increasing numbers of genetically altered species. The intended purposes of mixing genes and hormones from differing species include enhancing research on genetic diseases, producing pharmaceuticals, improving and increasing plants and animals for food supply and, quite obvious, the increase of corporate profits. While these are not unworthy motives, they do raise questions for intense debate within the international scientific community and among those whose main interests are money, ecology, animals, philosophical ethics and religion. All use political means to influence legislation and policies.

Representing the last category religious bodies, such as councils of churches, since 1987 have urged a moratorium on the patenting of organisms. Their concerns are varied: economic protection for farmers, animal growers, and certain poor nations; respect for animals; divinely given relation between humans and animals; and primarily, the possible detrimental effect of an increasing reductionist, mechanistic conception of human life. The last mentioned concern has been intensified by a proposed policy allowing the patenting of hundreds of genes in fragments of DNA even before it can be known what their function is.

It is now quite evident that the protestations of religious and social organizations have been ineffectual in their attempts to influence government policy and national practice. The issue is so very complex as well as remote from the experience of most citizens that it does not command much public debate. But for many professionals in molecular biology and biotechnology, inclu-

ding the corporate entrepreneurs and investors, it is a concern of great magnitude.

One thing which the problem of patenting makes clear, however, is that the ideal of freedom of inquiry and research in genetics becomes less actual as the dimensions of commercial production increase.

LEGISLATIVE FALLACY

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Introduction

After expressing a fervent devotion for Human Rights, some Recommendations of the Council of Europe, and in Spain Act 35/88 on Assisted Reproduction Techniques and Act 42/88 on the Donation and Use of Human Embryos and Fetuses or their Cells, Tissues and Organs, which are analyzed ahead, use a terminology that hinders comprehension of the values they transgress. The study of these texts has allowed me to discover or notice what I have called a «legislative fallacy». The subtle strings of the fallacy are strummed by scientific, therapeutic, economic and political interests. The dignity and life of man are put at the service of science and the human essence is endangered. To where is this inversion of values leading us?

The meaning of the term fallacy in philosophy, according to Ferrater Mora, is akin to that of sophism. A fallacy is an apparent argument, for it is not a genuine argument, or, at least, it is not a good argument. Neither a sophism nor a fallacy constitute valid forms of reasoning and the conclusions to which they lead are therefore false. A greater intent and desire to confuse the opponent or defeat the adversary is generally attributed to sophisms than to fallacies. Fallacy sometimes consists of a simple error or

imprecise reasoning. For the above-cited author, «as the sophist produces in the course of his sophism a similar type of argument, there is no reason for establishing a distinction between sophism and fallacy» [1].

In my opinion, the concept «fallacy» may be considered to include certain arguments whose line of reasoning does not directly lead to a stated conclusion, but which nevertheless arouse in their audience a predisposition to accept other subsequently expressed statements which contain errors or untruths.

In what does this fallacy consist?

1. The aforementioned laws were not enacted by means of the Constitutionally required Organic Act. They were approved by Parliamentary Committees and not by a Plenary session.

2. The Preamble or introduction to some of the Recommendations of the Council of Europe, and to the Spanish laws analyzed herein, propose as «should be» consistent with respect for the dignity of the person and the rights inherent thereto in accordance with the Declarations of Human Rights. However, this «should be» is contradicted in the text's ensuing sections, and the untruth is gradually heightened.

3. An error is induced through manipulated language and the use of euphemisms which conceal inadmissible actions. New terms are invented and over-generalizations are used.

4. An understanding of the laws is hindered because the mandate is dispersed over several sections which must be interpreted in *sensu contrario*.

5. Many experts are summoned but the institutions whose prestige and competence would allow them to issue authoritative decisions are not included. Left out are certain areas of knowledge such as psychology, psychiatry, and paediatrics, which could counsel against those aspects of the law of more far-reaching consequences.

6. A consensual civil ethics is proposed, supplanting the essential values of ethics.

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[1] Ferrater Mora, J: *Diccionario de Filosofía*, volume II, Alianza, Madrid, p. 1120, 1990.

Act 35/88 on Assisted Reproduction Techniques (hereinafter A/R) and Act 42/88 on the Donation and Use of Human Embryos and Fetuses or their Cells, Tissues and Organs (hereinafter Donation and Use of Human Embryos), epitomize the foregoing points. They were not enacted in accordance with the Organic Act procedure set down in the Constitution, but by Committees, without obtaining a consensus of the absolute majority. Section 166 of the current Criminal Code Bill makes reference to the «legally authorized circumstances» for the «donation, utilization or destruction of human embryos and fetuses or their cells, tissues or organs».

As is known, the Preamble or Statement of Purpose constitutes the introductory part of a law. It is a declaration of the legislative intent developed in the normative portion of the text. The lawmaker makes what we may call a «normative promise», which then takes shape and acquires the force of law in the ensuing provisions. The principles which are to govern the law are set down, to such an extent that ambiguous provisions are often construed by referring to the Preamble. A reader studying the law follows a natural mental course from the Preamble to the operative portion of the law. This course implies that the intentions declared in the Preamble are projected into the sections that there follow because, in a sense, the expository or descriptive portion lays the groundwork for the operative or prescriptive portion: the mandate.

A legislative fallacy has been committed because the «should be» of the mandate does not conform to the «should be» of the Preamble. In saying they do not conform, I am not referring to nuances or secondary questions, but that they are opposed, that the «should be» of the Preamble contradicts the «should be» of the mandate, cloaked in euphemisms and gratuitous affirmations.

How is it possible that the reader not notice such a flagrant contradiction? Therein lies the fallacy: the disposition and mental attitude of the reader are conditioned because he presupposes that the «should be» of the Preamble will be necessarily reproduced in the law's operative provisions. A favourable disposition dispensed to the lawmaker's stated intention is thus maintained throughout the text of the law. This is why the reader does not grasp the actual mandate, dispersed over several sections, or realize that the provisions must be read in *sensu contrario* if their genuine meaning is to be ascertained, or recognize the euphemism that conceals the person, or the improper use of terminology. Referring to the Act on Assisted Reproduction Techniques, Sancho Rebullida has stated: «The law referred to herein offers flagrantly unconstitutional aspects notwithstanding the euphemisms it uses and despite the recital of general principles con-

tained in chapter II, many of which are openly dropped by the rest of the text's sections» [2].

Background

Antedating both laws was Recommendation 1046, adopted on September 24th 1986, on the utilization of embryos and fetuses for diagnostic, therapeutic, scientific, industrial and commercial purposes.

This Recommendation, in the first 13 points of its introduction, recognizes human life as beginning at fertilization (5 and 8). It holds that the human embryo and fetus shall in all circumstances have the benefit of due respect for human dignity (10).

The rules proposed by the Recommendation are found in its Annex. They allow research with inviable embryos notwithstanding that, according to the statements contained in the abovementioned introductory part, such embryos are living human beings –human beings that will be used for the benefit of science. In this conflict of values research is placed before human life, and viability before the right to life.

There is a contradiction between affirming that the embryo shall in all circumstances have the benefit of due respect for human dignity and allowing research on the embryo.

Recommendation 1100 of February 2nd 1989 on the utilization of human embryos and fetuses in scientific research, like the aforementioned Recommendation, allows scientific research with inviable embryos. It advances one more step in the degradation of human life by allowing experimentation with living fetuses considered inviable. Inviability is to be determined by intrinsic defects of the embryo and fetus. Immaturity is excluded as a cause of inviability, though it is admitted under Spanish law.

ACT 35/88 A/R. In the Preamble the law seeks to «seduce» the reader, extolling progress and human creative capacity: «Technical advances have opened possibilities and hopes for the treatment of infertility: some 700,000 married infertile couples of childbearing age could benefit from embryo transfers in 40 percent of the cases and artificial insemination in 20 percent». Concern is voiced over the consequences of these techniques that can «touch off a diaspora whose implications arouse primarily social,

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[2] Sancho Rebullida: «Informe acerca de la posible inconstitucionalidad de la Ley sobre Técnicas de Reproducción Asistida 35/88» [Report on the possible unconstitutionality of Act 35/88 on Techniques of Assisted Reproduction], responding to an inquiry by Acción Familiar.

ethical, biomedical and legal fears». The Preamble affirms that «scientific and technological research should continue its expansion and progress limited by its collision with human rights and the dignity of the individual, which cannot be renounced». Further ahead it repeats that «actions must be taken from the standpoint of respect for the fundamental rights and freedoms of man, strictly for the benefit of human beings». These are matters entailing an enormous responsibility, it state, and it «will not always be possible or right to do everything that can be done». Could there be any more respectful attitude as regards human dignity and values than this, any greater desire for their protection? The law declares that «human beings have given themselves the resources to manipulate their own heritage and influence it through modifications». It is not man who can influence and modify his own heritage; in any event, it is certain scientists who can influence and modify the heritage of other persons and thereby manipulate their destiny. Do we have here another form of man's domination by man? [3]

The sections containing the law's provisions, however, do not express these concerns or fears or respect for rights, freedoms, and individual dignity. Human beings are degraded to the status of things, of objects at the service of scientific and economic interests. The degradation is achieved gradually, step by step. The term «pre-embryo» is already adopted in the Preamble, applied to the first 14 days of life of the fertilized ovum. According to geneticists and embryologists this term has no scientific basis. It is a tautology, «a change of words to justify a change of attitude» [4].

The introductory Statement of Purpose attempts to justify the term «pre-embryo» with the assertion that «prior to implantation, the embryo is still in the uncertain phase, and its existence may be ascertained after implantation». Ontology is confused with epistemology. It is the equivalent to saying: I am not aware of its existence, therefore it does not exist. The «scientific authority» (?) of the German Supreme Court is invoked, without taking into account the Human Rights Declarations subscribed by Spain, or the opinion of experts who declare that human life must be respected from the moment of conception (for example, the World Medical Association, Geneva 1948 Resolution, Oslo 1970...) or of many others with sufficient professional competence

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[3] Vila-Coro, M. D.: «El concebido no nacido en el orden jurídico» [The unborn child and the legal system]. Doctoral thesis no. 115/91, published by the Complutense University of Madrid, 1991.

[4] The professors of genetics Drs Lacadena, Lejeune, Puerta and Bompiani have so stated in the Workshop on Technology, Man and Science, organized by the IUVE and the Complutense University of Madrid, October 20th-22nd 1992.

to rule on the question. In short, the opinion of the experts was not taken into consideration.

In the Statement of Purpose the unborn fetus is termed «biological material» and is said to be «that development which spans from the moment the ovum is fertilized through to birth». It goes on to pose «the necessity of defining the legal status of embryonic development», a gratuitous affirmation that induces error, because such legal status is perfectly defined in the Civil Code. Section 29 of the Civil Code provides «the conceived [embryo] shall be considered as born for all purposes for which such consideration is favourable thereto». As can be seen, the degradation of the dignity and concept of the human person is progressive [5].

With respect to assisted reproduction and single women, which the law allows, the Statement of Purpose states that «from a standpoint of respect for the rights a woman to found her own family in the terms set down in international agreements and accords for guaranteeing the equality of women, the law must eliminate all limits which undermine her desire to procreate and constitute the type of family she freely and responsibly chooses».

«Against this it may be argued that responsibility means commitment, commitment to oneself and to others. Commitment refers to certain principles, be they ethical or legal ones. If limited to personal demands, it is not responsibility but arbitrariness. Women cannot establish types of families different from those allowed under our legal system, which constitute the foundation and structure of our western society. In no case can there be justification under the pretext of respect for women's rights for homosexual unions or other deviations from human nature, or single-parent families be justified, as those are not suitable environments for development of the child's personality. Suppressing the limits which the laws impose on this freedom to constitute new types of family does not undermine the will to procreate. What they undermine is none other than the foundations and structures which sustain and maintain society» [6]. Observe how the terminology employed in the Statement of Purpose tends to create confusion.

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[5] Camacho Zancada, B.: «Técnicas de Reproducción Asistida» [Techniques of Assisted Reproduction]. *Ventiuno Revista de Pensamiento y Cultura*, Autumn 1991, n.° 11, pp. 25 and ff.

[6] Vila-Coro, M. D.: «Los derechos del menor en la nueva genética» [The rights of minors in the new genetics], *Revista General de Derecho*, Valencia, p. 2491, 1992.

What does the operative part of the Act say?

The following examples will suffice to demonstrate the points made above [7]. The scope of the Act is defined as covering the regulation of techniques for assisted reproduction «when they are scientifically and clinically indicated» (section 1). Further ahead «... their fundamental purpose is medical treatment of human sterility». Note how there are no therapeutic effects in assisted reproduction in single women or when an anonymous donor is involved. The sterile progenitor remains sterile, his incapacity not remedied in the least. The donor is not cured; his generative functions are just supplanted. Hence, these techniques are not «scientifically or clinically indicated». Error is once again induced by the inappropriate use of language.

Nor are there curative effects in «sex selection for therapeutic reasons»

No such effects are produced, and even less so in cases of diseases transmitted by someone who does not suffer the disease but passes it on to her descendants. In the case, say, of haemophilia or colour blindness, gametes are so selected as to engender a female and thereby, it is argued, avoid the illness, when what is actually being accomplished is the procreation of an individual who will not suffer but transmit the disorder to her children. Where are the therapeutic effects? There are none, presuming that gametes and not embryos are selected; if embryos not belonging to the target sex are discarded, the «therapeutic effects» consist of «eliminating» the patient.

Lejeune remarked that «in addition to insemination by a donor to fill in for marital absence, nowadays we speak of a "carrier mother" inseminated by the partner of a sterile women to whom the baby is delivered nine months later in exchange for a sum of money. The terminological mastery achieved deserves to be highlighted; thus a man who agrees in advance to abandon his paternal duties we call a "donor", and a woman who engenders an adulterine child for subsequent sale we call a "mother"» [8].

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[7] See my article, ibid, which contains a detailed analysis of the Act.

[8] Lejeune, J: *Biotecnología y futuro del hombre: la respuesta Bioética*, Eudema, Madrid, p. 106, 1992. See López Quintás: «La manipulación del lenguaje» [The manipulation of language]. In order to garner support for its decriminalization, abortion has been termed «eugenic», «therapeutic», «ethical». The term «eugenic abortion» is another eloquent example of not just improper but contradictory use of a term. The Greek term *eu genesis* means well born. Thus, if the fetus is to be born with grave physical or psychic handicaps, the good *genesis* prescribed by the law is death (section 417 3rd bis Criminal Code). Abortion, or «voluntary interruption of the pregnancy», is also present in the Criminal Code as the consequence of an act constituting rape. Such cases are termed «humanitarian or ethical» abortions, in which it is the innocent fetus

New terms are invented

The operative part of the Act does not recognize the right to life of the pre-embryo (term which is introduced in the Preamble). Hence, excess embryos engendered by means of *in vitro* fertilization can be destroyed with impunity. These are not embryos suffering some type of deficiency, but simply ones which have been intentionally produced in excess numbers with full knowledge that they would not be implanted in the mother's uterus. The law also requires those existing more than 14 days in the laboratory to be destroyed also.

This is the first degree of impunity for acts against human life: the pretext is not qualitative; it is not because they present deficiencies (as is the case in so-called «eugenic» abortions). Here the rationale is quantitative: overpopulation (?). As will be seen ahead, the impunity heightens until reaching human life independent of the mother –the life of the newborn child.

The Criminal Code Bill currently under debate allows the «manipulation of human genes provided that the vital constitutional type is not altered». In order for alteration of the «vital constitutional type» to be punishable under to section 164-3, such alteration must have been the result of «grave negligence». Read in *sensu contrario*, if it is not the result of grave negligence, then it is not an offence. The expression «vital constitutional type» has no scientific meaning. Its introduction opens the door to genetic manipulation, and not for the purpose of eliminating or diminishing serious handicaps or disorders.

Arguments that lead to the absurd

Advocates of destroying or eliminating embryos assert that women spontaneously lose a great number of fertilized ova in early miscarriages. If that occurs in nature, they argue, it is only logical that some embryos be lost in medical treatment. This argument is as absurd as saying that since in nature all patients die sooner or later, why can't the doctor also let them die.

As an example of incongruity suffice it to once again cite the Draft Bill for the Criminal Code. According to section 162, causing harm to a fetus is punishable with from 1 to 4 years of prison and disqualification of from 1 to 6 years. Nevertheless, according to section 166, and its reference to Acts 35/88 A/R and 42/88

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whose life is taken, not the criminal, as might otherwise be presumed. The ethical position is opposed to the act of killing. Not even in legitimate self-defense is taking the life of the aggressor considered ethical; it is only tolerated ethically as an exception.

Donation and Use of Human Embryos, embryos and fetuses can be destroyed with impunity.

«Sensu contrario»

Included under the appealing heading «Diagnosis and Treatment», section 13.2 of Act 35/88 A/R is the one which most blatantly violates the fundamental rights of the human person. It reads as follows: «Any intervention on the living embryo or fetus in the uterus, or on the fetus outside the uterus, if it is viable, shall have no therapeutic purpose other than the promotion of its wellbeing and to favour its development». This should be interpreted in *sensu contrario* and stripped of euphemisms in order for its true meaning to be captured. We then see that a living fetus outside the uterus can therefore be used for therapeutic purposes that do not promote its wellbeing (the transplant of organs for instance) so long as the fetus is considered inviable. It should be noted that a living fetus outside the uterus is no longer a fetus, but an autonomous and independent life: a newborn child. That newborn child can be «used» if he or she is not considered viable. Its organs, structures and tissues may be extracted for grafting into other persons, for fabricating medicines... Any newborn child could be subjected to such treatment, as the criteria for viability are subjective judgements. Unlike Recommendation 1100 of the Council of Europe, it is not necessary for them to suffer from malformations, as has already been mentioned.

ACT 42/88, Donation and Use of Human Embryos... In case there was any doubt as to the interpretation of Act 35/88 A/R, two months later Act 42/88 on the Donation and Use of Human Embryos... was approved. Section 5.4 thereof provides: «Fetuses expelled prematurely and spontaneously, and considered biologically viable, shall be clinically treated with the sole purpose of favouring their development and vital autonomy». Again, read in the negative, inviable fetuses will either not be given clinical treatment or be given clinical treatment for other purposes: research, experimentation, utilization of their structures... Likewise read in *sensu contrario*, section 9.2e does not consider experiments with non-viable living fetuses and embryos to be punishable.

It is up to government to establish the criteria for determining viability or non-viability outside the uterus. Today, these criteria remain undefined. In their absence, could a scientist who judges a newborn child to not be viable and therefore uses that child as an organ donor be convicted? In the event that a conviction was produced, the offenses and sanctions are set down in chapter IV of the Act: they are not considered as criminal offenses, but simply administrative sanctions provided for in the General Health Act.

Viability is a prognosis as to the possibility of future existence, and therefore as uncertain as all prognoses. Yet, it takes precedence over the right to exist in the present. Health is a new statute taking priority over the right to life.

Civil ethics

The Preamble to Act 35/88 A/R states that the acceptance or rejection of the techniques regulated thereunder «should be reasoned on the basis of proper information to the patient, and be produced without regard to partial interests or ideological, denominational or party pressures, grounded solely on a civic or civil ethics not devoid of pragmatic components, the validity of which lies in the acceptance of reality once it has been borne out by rational criteria at the service of the general interest; an ethics, in short, which is in keeping with the majority feeling and constitutional contents, can be adopted without social tensions, and is useful to the legislature in defining positions or passing laws».

Proper information is thus considered a preliminary question to and a presupposition of any decision. This Act, on the contrary, does not facilitate proper information, due to euphemisms and the drafting of its operative portions.

Partial interests

It is perfectly legitimate for human actions to be motivated by personal interests, provided no third parties are thereby harmed. The Preamble is «much more altruistic» and rejects personal interest. However, its provisions allow heterologous assisted reproduction in the single woman or after the death of the husband. These situations protect the interests of the parents, donor, or the single woman at the expense of the child. They condemn the child to legal orphanhood, deprived of historical roots, exposed to consanguineous unions and to suffer diseases which are latent in the donor.

Civic or civil ethics not devoid of pragmatic components

Utilitarian and consensual ethics is inconsistent with the philosophical concept of ethics. Ethics or moral law is the human activity by which values are realized: good, justice, righteousness, values which transcend the subject and impose a «should be». Moral norms are *a priori*, preceding experience. How can the term ethics be applied to the «majority feeling»? The majority feeling may respond to circumstantial, crisis or even pathological situations. On occasion, societies experience difficulties of a diverse nature that can somewhat justify moral norms being interpreted with criteria specific to the situation

at hand. It is akin to what in law is known as «state of necessity»: these are attitudes of a person whose conduct deviates from what is legally ordained but who cannot be required to have acted differently (such as in the case of uncontrollable fear, for instance). History also abounds with examples of societies undergoing disintegration and whose customs become degraded. That in no way means that moral laws are no longer applicable just because they are no longer obeyed. And even less that the society is therefore legitimated to dictate its own moral norms. Moral norms are approved because they are just; they do not become just because they are approved by the majority. Society imposes legal norms and social custom, but moral laws are *a priori* and transcend the subjects for whom they are intended.

Majority feeling

Where is this majority, considering that only the amendments to the Act proposed by the socialist party parliamentary group were accepted? This is certainly an ethics born of party interests.

Lastly, there is the appeal to «constitutional contents». And this is where the most flagrant contradiction appears. The Preamble and introductory articles to the Spanish Constitution set down the values and principles which inspire our legal system: justice, equality and liberty. Article 10 extols respect for human dignity, for man's inherent rights and for the free development of his personality as a prerequisite for political order and social peace.

Some currents in legal thought still uphold the positivism and relativism of moral norms. The name civil ethics or consensus ethics is given to the new positivist version they wish to implant. It is said that «there is an efficacious means for rooting and consolidating pluralistic co-existence: the conscious, aware participation of all individuals and all groups in social life. Critical and accountable participation is the effective antidote against fanaticism and the social violence it spawns [...] Civil ethics constitutes the genuine fabric of a defanaticized and non-violent society. The civil-ethical project in which everyone collaborates breaks down and neutralizes violent fanaticism and fanatical violence» [9].

The technique for discrediting those who defend *jus naturale* principles consists in radicalizing their opinions and labelling them as extremists and fanatics. Gratuitous affirmations are put forth, certain arguments are generalized and used as an umbrellas to shelter others which could not stand alone. The consensus proposed by advocates of civil ethics is not seen in reality. There is no effective collaboration in legislative tasks; it is not the majority by

[9] Vidal, M.: *Bioética*, Tecnos, Madrid, 1989, p. 195.

Parliamentary Committees that define the ethical values on which legal provisions are to be based. A group holding a parliamentary majority will only accept amendments coming from its own group. This is what occurred with the Act on Assisted Reproduction Techniques, where only amendments made by the Socialist Group were taken into account, demonstrating that «the conscious, aware participation of all individuals and all groups in social life» is utopian and not practised in reality. And even if it were, the objective criteria of ethics cannot be replaced by bargains adopted by a society at a specific historical moment.

As Cardinal Ratzinger has observed «those who demand effective protection of life are repeatedly attacked with the argument that they are trying to force their moral ideas on the rest, on those whose conception of man is completely different from their own. Such things should not be done in a pluralistic society. This argument is absurd. He who is convinced that certain beings are persons has the obligation of fighting for their rights. He who fights against slavery, convinced it is inhuman, cannot be expected to respect the convictions of the slave-owner. Rights, if their existence is admitted, are the foundation for each human being's autonomy in relation to the moral judgement of the rest» [10].

What interests strum the subtle strings of the fallacy?

Are there underlying interests that favour certain options?

Live embryos have mainly been used for diagnostic and therapeutic purposes to investigate the development of certain diseases, the reasons for miscarriages, and congenital malformations. At present, still in the experimental stage but with promising prospects, embryo and fetal tissue can be grafted in order to cure or alleviate diseases such as Parkinson's, Huntington's, and Alzheimer's. Rejection is averted because fetal cells are by nature more readily adaptable to the patient's tissues. Moreover, they are «totipotent», that is, they can develop into cells of the brain, liver, kidney or any other part of the body.

According to Testart [11] spare tissue banks will be in use in the near-term future. These consist of surplus embryonic tissues obtained by dividing the embryo, implanting one part in the embryo and maintaining the other in the laboratory for two or three weeks, later freezing it in order to have spare tissue available for

[10] Ratzinger: *Bioética*, Rialp, Madrid, 1992, p. 73.
[11] Testart, J.: *L'ouef transparent*, ISBN 2-08-081157-6, 1986, pp. 135-137.

repairing the twin «brother's» organs without the risk of rejection.

«In Bordeaux, doctors used, with utmost secrecy, intact human fetuses that had been surgically extracted whole. After hysterectomy, these temporarily alive human fetuses were fragmented: the extracted pancreases were cultured in an artificial nutrient medium in order to facilitate renewal of cellular activity so they could reach the insulin-producing stage. In Lyon, researchers removed the liver from fetuses. In other laboratories, fetuses are decapitated and their heads used for the study of the cerebral gliacyte metabolism. One may savour the suggestive art of Pierre Jouannt, who clarifies that this is not done for pleasure; certainly not, not for the fetuses pleasure at any rate. There also exists, in Great Britain, a fetus tissue bank drawn on by French doctors for carrying out their tests. One should not be startled to learn that embryos that have died natural deaths or as the result of abortions have been used for commercial purposes for years. The detention at the French-Swiss border, of a refrigerator lorry loaded with human fetuses revealed the existence of a market in embryos. Originating in central Europe, they were destined for France to be used in the fabrication of skin-rejuvenating beauty products sold at very high prices. No comment!» [12].

«... culturing embryos would allow the preparation of spare parts, which would be used later for the treatment of children and adults. In particular, study is under way of the general procedures for bone marrow and other tissue grafts. If it is true that these grafts can be very useful –such grafts from volunteer adult donors are in fact already employed– specimens may only be taken from very developed fetuses, that is, those with several weeks of intrauterine life!» [13].

The abortion business generated several million dollars per year for the abortion clinic managed by Dr Nathanson, by his own admission. He has also spoken of the threat of «scientism», of scientists who collect the fetal parts of children from abortions and do business with them: «This is a flourishing trade in the United States, it is an exchange of parts; they buy those pieces from abortion clinics and sell them to research clinics» [14].

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[12] Brugues, J. L.: In *Revue Thomiste*, vol. 88, no. 1 (1988). The author was not speaking from memory; he cites his source in notes 174 and 175. Quoted by Basso: *Nacer y morir con dignidad Bioética*, Depalma, Buenos Aires, 1991, pp. 295-296.

[13] Lejeune, J.: «Genética, ética y manipulaciones» [Genetics, ethics and manipulations]. *Iatria*, Buenos Aires, nos. 176/177, 1986, p. 248. Quoted by Basso, ibid, p. 297.

[14] Dr Nathanson: Paper presented at the Congress «Juventud ¿Creyente or Atea?» [Youth, Believers or Atheists?], IUVE, December 21st and 22nd 1987, Madrid.

In a specific reference to the Act on Assisted Reproduction Techniques, Pantaleón quotes Robertson: «One group of citizens will be overjoyed by the promulgation of Act 35/88: doctors who participate or who propose to participate in the future in that great business fortunate enough to benefit from the free publicity into which the infertility industry is quickly being converted». He goes on to allude to the «absolute disdain for the fundamental rights of the future beings born of Assisted Reproduction techniques, which have guaranteed gamete and pre-embryo donors the utmost anonymity, averting the most serious risk of diminished flow of the raw materials needed for the business to prosper» [15].

State of opinion

Is there a sufficiently representative state of opinion that agrees with the aforementioned interests? If there is a widely held belief along these lines, we have to think that it could be the product of propaganda activities. Propaganda is scientifically designed to reach the subject and capture his will. The enormous sums invested in advertising firms, the specialized background of their prime movers, their highly refined techniques, etc., are all rather startling.

Techniques aimed at persuading consumers involve not only advertising experts, but sociologists and psychologists who know how to achieve loyalty –sometimes conscious, sometimes unconscious– to their products. Appeals are made to rational factors, though irrational ones are the most effective, because they correspond to biopsychological mechanisms. They pretend to make up for individual frustrations or inadequacies and appeal to different layers that interfere with or supplant rational discourse (for example, censers for the ego: «for men only...»).

Nowadays subliminal advertising has attained gigantic proportions. In the United States, cassettes are sold containing subliminal messages in the form of orders directed at making the listener adopt certain behaviour or attitudes that promote the development of his personality: quit smoking, build up self-confidence... The cassettes contain music, preferably classical music. The messages are recorded so as to be inaudible in normal conditions: the listener hears the music only. The words are completely hidden because they are recorded at frequencies which are inaudible to the cons-

[15] Pantaleón, Fernando: «Contra la Ley sobre Técnicas de Reproducción Asistida» [Against the Act on Assisted Reproduction Techniques], *Jueces para la Democracia*, December 1988. Reberlson quote, *S. Cal. L. Rev.* 59, 1986, 946.

cious mind. The sale and promotion of such cassettes is permitted, they are perfectly legal.

Technically directed propaganda can achieve changes in institutions, ways of life, customs. It brings on social upheavals and revolutions, it overthrows governments. This phenomenon benefits from the mimetic tendencies of human beings. The propensity to imitate makes it easier for the different shibboleths a society generates to be accepted. The mass media filters into our homes, surprise us in our most intimate shelters, precisely in those moments when we have deactivated our workaday alert and are placidly relaxing, with no barriers or filters to sift and ponder the information. That is why statistics on suicides are not generally disclosed, otherwise the example could spread to certain parts of the population. The same occurs with new forms of crime (arson in mailboxes, suicidal drivers, poisoning of products in supermarkets...).

Can we be sure that we have not been contaminated to some degree or other by that pollution which spikes the rarefied air we breathe?

Consequences of the fallacy

As a corollary to the above points we might echo the words of Serrano Ruiz Calderón: «Primarily for reasons of economic or political utility, acts contrary to the dignity of the human person have been justified by means of the procedure of reducing the definition of person. That is, excluding a greater or lesser number of human beings from legal protection [...] The historical effects in this regard are unquestionable. Slavery which had disappeared in Europe is re-implanted in America, denying the imported negroes the status of person; not just exploitation, but the extermination of entire races is likewise justified by classifying them as subhuman, as occurred in the American prairies. The final leap that is recent in our historical memory is the application of technological efficiency in an entire continent to free us of the unfit, the Jews, Slav intelligentsia, etc...» [16].

In order to avoid such situations the peoples of the world come together, international bodies are formed, and supranational treaties and commitments are subscribed. Declarations of Human Rights and modern constitutions enshrine universally recognized ethical principles. Panegyrics are offered to human dignity, which in our Constitution is extolled as a foundation of political order

[16] Serrano Ruiz-Calderón: *Biotecnología y futuro del hombre: la respuesta Bioética*, Eudema, Madrid, 1992, p. 91.

and social peace. Liberty and equality are set forth as supreme values of the legal system of justice (article 1). The right to life and to physical and moral integrity is recognized. Article 10.2 expressly cites the Universal Declaration of Human Rights and the international treaties and agreements signed by Spain as references for the interpretation of the fundamental rights and freedoms recognized in the Constitution.

As is known, notwithstanding the solemn declarations that protect them, fundamental rights are in fact violated with great frequency. Vintila Horia alludes to «the crimes perpetrated in the name of liberty and equality in a holocaust as universal and much more real than the Declarations» [17].

The situation now is much graver, for it is the laws analyzed above which are institutionalizing such violations. We have returned to techniques of the totalitarian state and the positivist outlook which have had such appalling consequences. As Recasens Siches has observed, «the totalitarian state is more than the invention of some major crimes, it is something which was allowed by virtue of having frivolously and irresponsibly ruined the legal-political axiology».

Health occupies a superior hierarchical position to which human life is subordinate, to such extent that the lives of embryos, fetuses and newborns are sacrificed in order to advance health. «The destruction of worthless life was a postulate first defended by Nietzsche and later by A. Hoche and K. Binding; its systematic, programmed application was masterminded by A. Guett. Arthur Guett was director of the Hitler regime's National Department of Hygiene. F.A. Wertham, in his work "A sign for Cain" [18], described the consequences of the Nazi-dictated "Law for the prevention of hereditary diseases" of 1933. Thus commenced horrors of all kinds. Euthanasia was not applied to patients with terminal illnesses or great suffering, but to the disabled and elderly [...] that utilitarianism in the judgement of human life won many disciples notwithstanding the many condemnations with which it met» [19].

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[17] Vintila Horia: «Los derechos humanos y la novela del siglo XX» [Human rights and the 20th century novel], Madrid, 1991, p. 124. See Blázquez: «Los derechos del hombre» [The rights of man], Madrid, 1980, p. 3; Duchacek: «Derechos y libertades en el mundo actual» [Rights and liberties in today's world] (translated into Spanish by O. Monserrat), Madrid, 1976, p. 15; Nino: «Etica y derechos humanos» [Ethics and human rights], Paidos, 1984, p. 13; Bobbio: «Presente y porvenir de los derechos humanos» [Present and future of human rights], *Anuario de Derechos humanos*, 1981, p. 9.

[18] Earner Paperback Library, New York, 1969.

[19] Basso: *Nacer y morir con dignidad*, Depalma, Buenos Aires, 1991, p. 242.

According to Robles «when certain groups demand as human rights aspirations or desires which are unjustifiable from the moral standpoint, they use words packed with symbolic prestige to defend what are nothing but their own interests». [20] To accept them as moral criteria, he goes on to say, «implies connecting rights with a system of values, with an axiological system of a general nature». The need for consistency in one's values is inescapable.

Conclusion

Human rights declarations and modern constitutions are founded on transcendental ethical values. The laws I have analyzed here, however, do not respect the dignity of the human person or his fundamental rights.

Our legal system contains a breach, a contradiction, a *legislative fallacy*, for notwithstanding that our Constitution contains clauses such as those found in articles 10 and 15, proclaiming human dignity and man's inherent rights, the right to life and to physical and moral integrity, laws like the ones denounced herein are nonetheless on the books.

The fallacy also manifests itself when the same legislature that ratifies the Convention on Children's Rights (adopted by the General Assembly of the United Nations on November 20th 1989 recognizing the rights of children and declaring the interests of children to be preeminent over all others) can also approve laws such as the ones I have cited here.

Either we are victims of a fallacy that has not allowed us to see the consequences of these laws or we have lost sight of our values, the fountainhead of morality, the perception of the human essence. An inversion of values has taken place. A new law, health, has come into force amid all the democratic salutes to fundamental rights. The right to life has been made subordinate to health and only those in good health can effectively hold the right to life. Science has also been catapulted to the upper echelons of the hierarchy. The desires of the parents and interests of the anonymous donor prevail over the child's interest.

Resolution number 3 of the Ministerial Conference held in Vienna in 1985 on the rights of man requested that the Council of Europe be the a point of convergence for biomedical issues. By

[20] Robles, G.: *Los derechos fundamentales y la ética en la sociedad actual*. Civitas, Madrid, 1992, pp. 26 and ff.

decision of the Committee of Ministers, the CDBI became the governing Committee in the field of Bioethics. The aim is to harmonize legislation in the member states.

In 1991, Recommendation 1160 advised that a European-wide Convention on Bioethics be drafted. The Council of Europe's *Forum* journal of February 1993 contains statements made by Marcelo Palacios, the Parliamentary Assembly's representative in the CDBI, Spanish socialist deputy, and chairman of the Subcommittee for Family, Health and Bioethics.

Palacios believes it necessary for rules be established in order to:

- Assure the protection of the individual and of society.
- Dispel fears and misunderstandings so that scientists may continue their work in the appropriate environment and, if possible, within a legal framework.
- Set down regulations against the misuse of science and technology, and preserve human dignity and physical and psychological integrity.
- Bring individual and social rights into harmony with scientific freedom, in order to prevent science from being hampered by arbitrary barriers.

I believe that any moralist or well-meaning citizen and even the Catholic Church itself would subscribe to these principles without any reservation. Will the provisions of the Convention that is to be drafted respect the above or commit yet another legislative fallacy?

RIGHT TO CONFIDENTIALITY: USE OF GENETIC INFORMATION

PRESENTATIONS

RIGHT TO CONFIDENTIALITY: USE OF GENETIC INFORMATION

Paula Kokkonen *

Director General of the National Board of Medicolegal Affairs, Helsinki. Finland.

Opening remarks

If I'm correct I have been asked to attend this meeting due to being former chairperson of the CAHBI, Council of Europe Committee on Bioethics, later called CDBI, Steering Committee on Bioethics.

The work of CAHBI

«The main objective of the work of CAHBI has been described as to fill the political and legal gaps that may result from rapid development of biomedical sciences». It is seen that the lack of common action from the part of the member States might result in a legal void with all of the inherent risks. Thus CAHBI has been producing and publishing reports and studies, organizing hearings, meetings and symposia as well as attending important meetings either in corpore or through representatives.

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* Moderator.

CAHBI has also prepared recommendations and CDBI is working on a Convention which is aimed at protecting Human Rights with regard to the application of biomedicine and human biotechnology.

It is still worth mentioning that all the Council of Europe's member States (29 when this is being written), when accepting a Recommendation in the Committee of Ministers, are supposed to adjust their legislation accordingly, unless they make reservations.

When speaking of the right to confidentiality and the use of genetic information I will focus on three Council of Europe Recommendations:

1. Prenatal Genetic Testing and Screening, Rec. R 90 (13),

2. Genetic Testing and Screening for Health-care Purposes, Rec. R 92 (3) and

3. The use of DNA-testing for Criminal Justice Purposes, Rec. R 92 (1).

Recommendation R 90 (13)

In Rec. R 90 (13), Principles 11-13 deal directly with confidentality and the use of genetic information. Principle 11 reads as follows: «In prenatal genetic screening, prenatal genetic diagnosis or associated genetic counselling personal data may only be collected, processed and stored for the purposes of medical care, diagnosis and prevention of disease and research closely related to medical care. Such data should be collected, processed and stored in accordance with the Convention for the protection of individuals with regard to automatic processing of personal data and Committee of Ministers Recommendation No. R (81) 1 on regulation for automated medical data banks.»

In Principles 12 and 13 it is stated that any information of a personal nature must be kept confidential and that the right of access to personal data «should be given only to the data subject in the normal manner required for personal health data in accordance with *national law and practice*. The communication of genetic data which relates to one member of the couple should not be made without free and informed consent of the former to the other».

In the explanatory memorandum it is stated that genetic data is particularly sensitive and confidentiality must be assured. Thus the collection and storage should be restricted for medical use and

controlled. The Recommendation *prohibits testing for research purposes alone.*

Recommendation R 92 (3)

The recommendation concerning genetic testing and screening for health-care purposes emphasizes that no benefits should be made dependent on undergoing genetic tests or screening and thus protects the individual against possible third parties requests concerning confidential information. (Principles 6 and 7).

The third part of the recommendation is titled «Data protection and professional secrecy».

As to data protection, reference is made to the Council of Europe's basic principles of data protection and data security laid down in Convention No. 108 of 28 January 1981 «and the relevant Recommendations of the Committee of Ministers in this field». This concerns both the collection and storage of substances and of samples and the processing of information therefrom. These activities are allowed for the purposes of health-care, diagnosis and prevention of disease and for *research closely related to these purposes.*

Principle 8, paragraph b. reads as follows: «Nominative genetic data may be stored as part of medical records and may also be stored in disease-related or test-related registers. The establishment and maintenance of such registers should be *subject to national legislation».*

In Principle 9 strict confidentality and *national legislation aimed at preventing the misuse of genetic information* are claimed.

The second paragraph of this principle contains the following: «However, in the case of a severe genetic risk for other *family members,* consideration should be given in accordance with *national legislation* and professional rules of conduct, to informing *family members* about matters relevant to their health or that of their future children.

In the explanatory text it is discussed that under existence of a serious risk for a close family member some derogations could be authorized by *national legislation.*

Genetic data should as a general rule be kept separate from other personal records.

Principle 11 deals with unexpected findings. As an example is mentioned incidental information of genetic lineage of the person concerned. As a main principle such findings should only be communicated to the person if they would be of direct clinical importance to the person or the family.

«Communication of unexpected findings to family members of the person tested should only be authorized by *national law if the person tested refuses expressly to release information even though the life of the family members is in danger*».

Concerning research, the main rule is that, collecting data and samples and their use needs permission from the person concerned, they should remain anonymous and are covered by confidentiality.

Recommendation R 92 (1)

The recommendation concerning the use of DNA-testing for Criminal Justice Purposes applies to «the collection of the results of DNA analysis for the purposes of identification of a suspect or any other individual within the framework of the investigation and prosecution of criminal offences».

It is presupposed as a main rule in Principle 3, «Use of samples and information derived therefrom», that samples collected for criminal justice purposes are not used for other purposes. The individual from whom the samples have been taken may, however, get the information they carry, if he so wishes.

On the other hand, «samples collected from living persons for DNA analysis for medical purposes, and the information derived from such samples, may not be used for the purposes of investigation and prosecution of criminal offences unless in circumstances laid down expressly by the *domestic law*».

The use of DNA samples for research and statistical purposes is acceptable provided the identity of the individual cannot be ascertained.

DNA analysis should only be carried out in accrediated and regularly supervised laboratories and institutions, which among other things, can guarantee adequate security of the installations and of the substances under investigation, and adequate safeguards to ensure absolute confidentiality in respect of the identification of the person to whom the result of the DNA analysis related (Principle 6).

Under Data protection is referred to previous Council of Europe Convention and Recommendations (Principle 7).

Principle 8, «Storage of samples and data», anticipates that DNA samples are not kept after rendering the final decision in the case for which they were used, unless it is necessary for purposes directly linked to those for which they were collected.

It is also presupposed that measures are taken to ensure that the results of DNA analysis and the information derived therefrom is deleted when it is no longer necessary to keep it.

There are again some exceptions to these main rules. They mainly relate to criminal investigations concerning serious crimes. Even in these cases strict storage periods should be defined by domestic law.

Concluding remarks

People have a fear, legitimate or not, that samples collected for DNA analysis might be used for purposes other than those for which they were collected. It is therefore important that rules are made to ease the fear of unlawfull use of samples and information derived from them.

As can be seen from the text above, many very important decisions have been left *for national legislation,* as the Committee, CAHBI (later CDBI), was not able to find noble solutions or a consensus. Discussions in the Committee have indicated that even those principles, that have been unanimously agreed upon and are verbalized in the recommendations, can be interpreted and materialized in different ways in our pluralistic European societies.

I have experienced that people, living on other continents, very often speak of Europe as one entity. The one thing that becomes obvious when participating in the work of the Council of Europe is that different traditions, cultures and schools of thought abound in Europe.

Paradox

Privacy, on the one hand, is greatly emphasized simultaniously as we, on the other hand, through genetics, recognize that we are not so independent of each other, and that we do posess a lot of information of each others through our genes.

De lege ferenda: analogy: pedigrees are drafted by lawyers in inheritance questions; would it be possible to accept the principle, that those relatives who can inherit you may also, without your permission, get genetic information concerning you, if it is urgently needed to save someones life or to prevent a serious illness? Should one, on some grounds, be able to cut someone off the information chain?

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CONFIDENTIALITY, PRIVACY AND GENETIC DATA

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Are human genetic issues so «special»?

Since 1992 the European Communities research programme on Human Genome Analysis, which had been a separate specific programme in its pilot phase (1990-91), has become part and parcel of the general EC Biomedical and Health (usually known as BIOMED) research programme: the human genome is now only a particular area of BIOMED (with more than 20% of the total budget).

This organizational change had two important consequences: first, that the Human Genome Project is by now an accepted part of biomedical research in the European Communities [1]; second, that

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* Keynote Speaker.

[1] In fact, the main opposition to the initial Commission proposal in some quarters of the European Parliament focused on the intended links of the research with *predictive medicine*. As regards future, it is now probable that a new general area of «Genomes» (the plural is important) becomes part of the basic biotechnology research programme (while Human Genome remains part of biomedical and health programme) in the new Life Sciences Specific Programmes soon to be proposed by the Commission in 1994: but this intended change reflects also other strategic and management concerns that we cannot discuss here. For the present BIOMED programme, cf. Council Decision of 9 September 1991, in *OJ* L 267, 24-9-91, p. 25.

the ethical, social and legal aspects of Human Genome Analysis now also become part of the general substantive area of Biomedical Ethics (which was allocated almost 4% of the budget in the BIOMED programme).

These management changes mean probably that, through a long (and yet un-finished) public discussion, policy-makers in the EC are coming to the conclusion that, after all, *there is not so much about genetic information that is so different from other forms of medical information.* That was, in particular, the conclusion of the ESLA Report which the Commission transmitted to the European Parliament and to the Council of Ministers in 1992 [2]: «the C.E.C. Programme Human Genome Analysis does not *per se* raise fundamentally new ethical or social questions».

I think other participants have already expressed in public the same opinion: perhaps we have all been putting too much weight on the ethical, social and legal issues of the Human Genome Project [3]. This has been probably the area of life sciences more open to ethical scrutiny in History. But the Human Genome Project amplifies problems that are already there, rather than raise any *new* problems. It is perhaps the right moment to concentrate on pragmatic, positive legal provisions.

The scientific and technological promises of the Genome Project are being fulfilled, in an accelerating way, as it was stated in the morning session. The gaps between information and understanding, and between diagnosis and treatment, are still wide, but cost/benefit audit and assessment of the public funds committed will become more positive as biomedical researchers will gradually be able to understand genetically cancer, heart disease, diabetes, mental illness and birth defects, and to the extent that gene therapy will be integrated into medical practice of tomorrow.

However, public enthusiasm for what new genetic knowledge can bring is still tempered by fears about how it might be used. Well,

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[2] Working Group on the Ethical, Social and Legal Aspects of Human Genome Analysis (WG-ESLA), Final Report. A ministerial meeting to transform the recommendations of the Report into Council Conclusions was foreseen for May 93 in Lisbon and later cancelled. Some of the Report recommendations on the *legal* aspects of future *applications* of research results, namely intellectual property rights, use of genetic information in the workplace, in relation to insurance, or in forensic practice, are discussed in other panels, so I will not comment on that here.

[3] That is also a main theme of the Proceedings of the Conference held in Houston, Texas, March 7-9, 1991 (see Mark A. Rothstein, Editor, *Legal and Ethical Issues raised by the Human Genome Project*, Health Law and Policy Institute, Univ. of Houston, Texas, 1991, in particular A. Capron, «Legal challenges of the Genome project», p. 69 and ff.

my thesis here will be that probably the best way to prevent genetic information from being used unfairly is to protect its privacy.

The conflict between privacy and the limits of confidentiality

From an European perspective, we should therefore begin by quoting Article 8 of the European Convention of Human Rights of 1950 (which has its precedent in Article 12 of the Universal Declaration of 1948):

- Everyone has the right to respect for his private and family life and his correspondence.

- There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the protection of health or morals, or for the protection of the rights and freedoms of others».

Here we have, in a nut-shell, all the essentials concerning the fundamental right recognized in the constitutions and laws of European democratic States and therefore also in Community law.

On the one hand, society must guarantee respect for privacy as essential to the individual's development. On the other hand, many limitations are listed in the Convention itself, so that privacy it not an absolute but a relative right. In particular, the protection of health is mentioned. In fact, the rights of many others –family members, fellow employees, the public at large– could conflict with the individual right to privacy. And in practice many health practitioners consider confidentiality just another «romantic myth», and this is probably why recent attempts to legislate (the US and in Europe; e.g. in Denmark) on genetic privacy have *not* been successful to limit either genetic tests and screening, or uses of genetic information.

However, medical confidentiality is still the standard safeguard to protect privacy and medical information. Responsibility in the use of personal medical information lies on the normal doctor patient relationship. The question again arises: is there something about genetic information that is different from other forms of medical information? This kind of issues will be discussed by further panels tomorrow: is it ethical or legal for an employer to require that

applicants and employees submit to genetic testing or disclose genetic assessments?

It could be argued that genetic information is perhaps the most personal kind of medical information. It affects present and future health, reproductive options, and the health of offspring. Personal genetic information should therefore be confidential, and one should enjoy a right not to be discriminated against on the ground of one's genetic constitution.

An individual's genetic make-up is unlikely to be directly related to the ability to perform essential jobs functions: or it could be information that the individual may not want to know.

We do not choose our genes, and information about them should be essentially private. No person should be subject to genetic testing without his or her knowledge: such genetic information should not be given to a third party without permission of the individual, unless such disclosure is essential to avoid harm to another person [4]. However, as we shall discuss in other panels, the voluntariness of disclosure protected by privacy legal provisions do not solve the real practical problems: confidentiality protection does not ensure access to health or life insurance, nor avoids discrimination on disability protection or employment. In order to protect the genetically disadvantaged against lack of access to education to jobs, to credit and to insurance, new public policy and perhaps anti-discrimination legislation could be necessary.

On the other hand, justifications for workplace genetic screening could probably include promotion of public safety and individual

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[4] The Guidelines for third party disclosure in the US President' Commission report *Screening and Counselling for Genetic Condition* are thus not very different from those being prepared in the Council of Europe steering committee presently drafting a Convention on Bioethics. The main provisions of the preliminary draft Convention of the Council of Europe are as follows (texts not yet agreed by the drafting committee):
«*Article 11.* Everyone has the right to privacy in the health field. Individuals are entitled to [access to] [know] any information collected about their health status. However, if individuals request not to be so informed they should have their wishes respected».
«*Article 16.* Tests which are predictive of genetic diseases shall only be performed for health purposes or scientific research».
«*Article 17.* The communication of results of genetic testing outside the health field shall only be possible if authorised by national law when there is an overriding interest».
Besides privacy, many issues, e.g. the right to know and the respect of a settled wish *not* to know, are concerned in these draft provisions. For further background (although limited to insurer/employer issues), cf. Zimmerli, «Who has the right to know the genetic constitution of a particular person?», in Chadwick *et al.*, eds, *Human Genetic Information: Science, Law and Ethics*, 1990 (Chichester, UK: John Wiley): 93-102.

health. Public safety is perhaps a legitimate reason to test when the genetic condition detected has a relationship to workplace exposures. In practice waivers authorizing physicians to disclose medical examination as they deem necessary, including to management, are a fact of life [5]. But here again, confidentiality protects the privacy of the person against dangerous stereotypes: even the reductionism or genetic determinism fostered by the very success of the Human Genome Project create wrong popular images, being shaped by press and media impact [6].

But in fact, family or other environmental, social, cultural and educational factors are stronger than genes to create moral responsibility or stimulate intellectual ability. This is also an additional reason to uphold the general principle of confidentiality for personal genetic information.

Individual protection and data bases

There is also a well-known clash of values around this issue, for which there are many particular European legal instruments (the world's first data protection law was enacted more than 20 years ago in the German Land of Hessen): namely, the potential conflict between the right of each individual to the confidentiality of his or her own genetic code and the needs of free circulation of information, in particular for scientific research, but also for epidemiology and health issues, etc. This free movement of medical and scientific data is of course enormously expanded by the informatics and telematics [7], and this is precisely the issue addres-

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[5] AIDS experience is often a pioneer for genetic ethical and legal debates: in the US, in particular, State (rather than federal) legislation deals with HIV-related medical records and protects (with very diverse standards) from discrimination, in order to encourage voluntary HIV testing; US Courts have found several values which can supersede medical confidentiality: individual therapy, public health and also protection of third parties (ranging from lover to employer): lives of children in danger are of course more important than a patient's privacy. And even R&D purposes (in particular for public-funded health-oriented R&D) should limit confidentiality. Cf. the brilliant presentation by Prof. Harold S.H. Edgar, «The Genome project and the legal right to medical confidentiality», in Rothstein, op. cit., pp. 197-221.

[6] As we shall see in yet another panel, even in forensic uses of DNA, a person's privacy should be respected. The release of DNA information on a criminal convict without the subject permission for purposes other than law enforcement should be considered a misuse of the information.

[7] That is the subject of AIM (Advanced Informatics in Medicine), a Research and Development programme of the C.E.C. Cf. CEC, *AIM 1992, Research and technology development on telematic systems in health care*, Brussels, 1992; J.N. Van Croor and J.P. Christensen (eds), *Advances in Medical Informatics*, IOS Press, Amsterdam, 1992, in particular the contributions of Lobato de Faria (358 ff.) and Christensens-Villasante (p. 387 ff.) on Data Protection and Confidentiality.

sed by both the Council of Europe Convention of 28 January 1981 for Protection of Individuals with regard to Automatic Processing of Personal Data (in particular in Article 6), and the new Commission proposal for a Council Directive in the same field.

The main reason for the latter text, proposed by the Commission in 1990 and recently amended, was that the 1981 Convention was too general and also that Member States applied it with differing degrees of protection, the Southern States in particular failing to protect adequately the individuals or even lacking any legislation at all [8]. Therefore, the 1993 single market in Europe could mean free movement of data without adequate protection (or the other way round, any movement at all being blocked ny national legislative differences).

As has often been the case in the bioethics field, the Council of Europe has set international standards and by contrast little has been accomplished in the Community [9]: but the new Community proposal could at least take account of developments in information technology and progress in medical science in the last decade.

The initial Commission proposal of 1990 has not been well received by many «lobbies» (including the employers and the banking sector) and the EP also required several changes, mainly to state the principle of informed consent, to control processing of

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[8] Spain has recently legislated at last, but still 3 Member States have no legislation at all and 5 have not ratified the Council of Europe Convention. On the Spanish Bill, cf. A. Pérez Luño, «La incorporación del Convenio Europeo sobre la protección de datos personales al ordenamiento jurídico español», *Informática y Derecho*, no. 17 (1989), pp. 29-43. (For a general comparative review, cf. Colin Bennett, *Regulating Privacy : Data Protection and Public Policy in Europe and the United States*, London, 1992) Of course, we cannot discuss here the *Constitutional Law* foundations. I will just mention, as background reference, that recent post-authoritarian Constitutions have more adequate provisions contemplating new technological challenges to privacy (e.g. Art. 18 of the Spanish Constitution, Art. 19 of the Greek Constitution, Arts. 33-35 of Portuguese Constitution) than older Constitutional provisions protecting privacy, from Nordic democracies to post 2nd world war (Germany, Italy): cf. also A. Perez Luño on that: «La protección de la intimidad frente a la informática en la Constitución española de 1978», *Revista de Estudios Politicos*, 1979, no. 9, pp. 59 ff. For the classical discussion on «Confidentiality» cf. Winslade, pp. 194-2010 in W. Reich, ed. *Encyclopedia of Bioethics* NY, Macmillan on 1978. I think Prof. Fletcher, who is here with us, is preparing a second edition of *the Encyclopedia*. We look forward to what he will say on «Confidentiality».

[9] Cf. J.P. Jacqué, «Liberté d'information» (p. 309 ff.) and G. Knaub, «Protection des données» (p. 365 ff.), and the Commentary by B. Loder (413 ff.) in A. Cassesse et al. *Human Rights and the European Community: The Substantive Law*, Baden-Baden 1991 (vol. III, Nomos Verlag). I presented a summary of those European standards in my article: «Confidentiality» for Fundación BBV, *Human Genome Project: Ethics* (Madrid 1992), 287 ff., in particular p. 291-92.

data concerning health or sexual life or other sensitive information, to control disclosure to third parties, to enhance right of access and to encourage professional codes of conduct [10].

However, even in cases where existing legislation with high levels of data protection is formally respected, medical confidentiality can be violated, as a recent case in France has shown: a Paris laboratory had to suspend a study into children born by artificial insemination using anonymous donors, which had been approved by an ethics committee headed by Prof. Changeux (himself Chairman of the French national ethics committee). But a further inquiry judged that by transmitting the names of the children, and also of the donors, without their consent, to researchers, national legislation had been infringed [11].

Finally, the Council of Europe, always active a the forefront of human rights, is now preparing a draft Recommendation on the protection of medical data. This raises some concern in its present drafting, as we will see. It makes important points, such as stating that «any individual should be entitled to expect that his genetic data are not disclosed outside his genetic line» (Principle 13.1). (In the draft Bioethics Convention, this has been changed to «his or her family»). The draft Recommendation also extends the principle of free informed consent for diagnosis, therapeuthic and preventive purposes; and it requires «appropriate safeguards» to processing of genetic data for other purposes, such as criminal offences. In particular, however, Principle 13.10 states that «genetic data may only be collected and processed for purposes such as employment and insurance if the data subject has given his consent *and as far as this is not prohibited by domestic law*». In fact, one could wonder whether the Council of Europe with such a provision, is not opening the way to national contractual trends which would then extend free movement of genetic information in the economic sectors, therefore seriously eroding the scope of the traditional confidentiality safeguards. If that were the case, the adaptation to technological progress would have meant a marked step back from classical privacy protection.

In conclusion, after some time of public debate, and even if significant international instruments are being drafted, one cannot be so sure that the ethical, social and legal aspects of the human genome programme will in practice mean a real progress of personal autonomy and fundamental liberties, at least here in Europe.

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[10] The modified proposal, together with the initial text, has been published in the *EC Official Journal*, no. C 311, 27 Nov. 1992, pp. 30-61.

[11] Cf. *Nature*, 361, p. 102, 14-1-1993. However, the French Comité Consultatif National d'Éthique had given a well-balanced opinion on genetic tests, family studies and data banks on 24 June 1991, underlying the rights to privacy and confidentiality.

In the research and clinical fields we have certainly important safeguards through ethics committees and professional codes of conducts. But it could also be helpful if lawyers and lawmakers played a positive role in defence of human rights concerning the challenges of new technologies, in particular in the privacy and data protection area.

THE RIGHT TO PRIVACY AND THE USE OF GENETIC INFORMATION

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Introduction

Quite possibly the two most unsettling scientific revolutions of this century have been in nuclear physics and what is today known as the Human Genome Project. An initial workshop on international cooperation for the Human Genome Project took place in Valencia from October 24th to 26th 1988. A second workshop on the same question (referring to ethical aspects of the project) was held in Valencia in November 1990. The legal aspects were likewise dealt with in Coimbra, Portugal in June 1992. The declaration of principles drafted in the second workshop included the following:

«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

* Keynote address.

faces technical obstacles and does not command ethical consensus. We endorse further discussion of the technical, medical, and social issues on this topic.»

In his introduction to the volume published by the Fundación BBV on the second workshop, Santiago Grisolía states the following:

«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 are 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.»

We must be prepared for the problems raised by the use of genetic information. 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. We must not forget, however, that no one chooses their genes and that the information they furnish *must be confidential.* No one should be genetically tested *without his consent* and the information obtained *must not be released to others* without the owner's permission, unless necessary to avoid harm to other people. «All these aspects», Grisolía concluded, «were discussed during this second workshop, which originated the II Declaration of Valencia.»

No one should be surprised that the subject evokes keen interest from jurists. Keep in mind that it is associated with eugenics and racial hygiene, though that means overruling individual decisions on having children and choosing a partner, and, even, in the Nazi genocide, sacrificing the right to life.

Specific issues are raised on the legal terrain: could job candidates or potential insureds be obliged to present their genetic map? Is this an invasion of privacy? Insurance companies already require a preliminary medical examination and a large part of personnel selection tests invade privacy. The Alcalá de Henares municipal government in a recent questionnaire queried job applicants as to their sexual behaviour (incidentally, a challenge to this practice was filed and upheld). Could a person's genetic map be investigated in the process of investigating a crime?

Scientific state of the question

When more than two centuries ago (1789) T. Robert Malthus announced the so-called «black theorem» on the clash between food resources generated on earth and humanity's progressive growth, a tremendous problem was raised. Malthus's proposed solution was of course «ethical abstinence», but discoveries made since that time have provided ethically and legally controversial solutions. At the individual level there is abortion for socio-economic reasons; at the societal level, the sterilization campaigns «forced or voluntary» currently under way in many countries; from the racist standpoint, blood purity laws and eugenic theories on the protection of the race or species. Vogt's book *Path to Perdition* was translated into Spanish in 1950. Its central idea was that the hunger suffered by many groups of people is a consequence of the earth's scarcity (low production) and of the human race's uncurbed reproductive appetite. His proposed solution was rigorous birth control, allowing the infirm and weak to die, thus dislodging the excess population struggling to barely survive to the benefit of the «privileged spectators». The world, in short, would be for guests of certain standing and not some crowded, jostling street fair for everyone. Some have said that Vogt should have a place in the gallery of enemies of humanity.

Since then advances in biotechnology has made «ethical abstinence» a solution for those whose consciences saw moral or religious problems in other methods. This advance can be briefly divided into the following stages: 1) artificial insemination; 2) embryonic transplants; 3) *in vitro* fertilization and 4) genetic manipulation. As long as these techniques were used with animals, society accepted them with certain gratification they could be the solution to the problem of multiplying food resources for growing populations. The problem, obviously, has been when these techniques have been applied to human procreation [1]:

[1] Perez y Perez, Felix: «El fascinante avance de las biotecnologías en reproducción animal» [The fascinating advance of biotechnologies in animal repro-

a) Artificial insemination of domestic animals began in 1779 with the investigations carried out by Abbot Spallanzani of the Pavía Athenaeum. Encouraged by the success of artificial insemination in flowers and fish, he experimented with fertilizing a female dog in heat with semen from a male canine. The female was successfully fertilized and bore a litter of normal puppies bearing resemblance to their progenitors. Since then artificial insemination has evolved in three different, complementary areas: semen collection methods, *in vitro* semen preservation techniques and techniques for fecundation (gametization) in the female. In recent years, artificial insemination has been the standard system for multiplication and reproduction of the bovine population. Now, as from 1990 artificial insemination began to yield its place to *in vitro* fertilization and embryo transplant methods.

b) Walter Heape of England is cited as the first to perform an embryo transplant in 1890. He extracted fertilized eggs from female rabbits and sheep a few days after copulation and immediately implanted them in females of the same species. As Professor Felix Perez has said, today «embryo transplants and artificial insemination represent a starting point for genetic manipulation in the service of livestock improvement and selection through pedigree tests».

c) *In vitro* fecundation technology dates back to 1951 and the research work of Chang, who achieved the first successful fecundation with rabbits in 1959. Curiously, the technology for *in vitro* production of animal embryos trailed advances in human medicine. This tendency, however, has been inverted to a great extent in recent years. But the news of the first human being conceived outside the mother's womb (ectogenesis), which headlined newspapers on June 26th 1976, represented the start of the revolution we are experiencing today, and of the need to re-evaluate the foundations of a good many legal principles: homologous or heterologous artificial insemination, rented wombs, *in vitro* fertilization, genetic manipulation, and so on, raise moral and religious, as well as legal, issues.

d) Reproduction biotechnology is currently focused on the promising field of genetic manipulation. Microsurgery applied to gametes and blastocysts can produce identical animals. Today cloning is a reality. This is known as «genetic engineering», whose utmost ambition thus far has been the production of

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duction]; Address upon entering the National Royal Academy of Medicine, Madrid, 1970. The summary included in this paper is taken from the data contained in this interesting work.

> transgenic or artificial animals. Androgenesis and gynogenesis are possibilities which, using male and female genetic material, respectively, allow us to obtain exact-copy animals. The outlook is unsettling. As Walter Gilbert[2] has said: «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 [...] 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 [...] 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 behaviour 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».

The misgivings aroused by the application of these methods in human beings should not be a cause for wonderment. Indeed, any other reaction would be surprising. As for the Catholic Church, Pope Pius XII, in his 1949 address to the International Congress of Catholic Physicians, stated «The active element of fecundation must never be procured illicitly through *unnatural* acts». In 1951 he would repeat: «Man cannot ethically dispose, assign or transfer his gametic components». Artificial insemination outside matrimony, which has been especially condemned by the Church, is a widespread practice nonetheless. In the United States (Georgia and Oklahoma) heterologous artificial insemination is allowed with the written consent of the husband. In other states (New York) it is considered contrary to public policy and morals.

The Vatican's Instruction on these problems, largely inspired by Cardinal Ratzinger, can be summarized as follows: The civil law shall not authorize artificial procreation methods which give to third persons (doctors, biologists, economic or government powers) that which is the exclusive right of spouses, and shall not legalize the obtaining of gametes from persons who are not legitimately joined in wedlock, or embryo, sperm or ovocyte banks.

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[2] Gilbert, W: «Sequencing the Human Genome: Current State», *Human Genome Project: Ethics*, Fundación BBV, 1991, pp. 45 and ff.

It should be pointed out that the position of other Christian Churches, although perhaps less dogmatic, is somewhat similar to that of the Catholic Church. J.L. Stotts has summarized the viewpoint of the World Council of Churches as follows: the organization *i)* 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»; *ii)* «draws attention to ways in which knowledge of an individual'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»; *iii)* «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»; *iv)* «proposes a ban on experiments involving genetic engineering of the human germ line»; *v)* «advises governments to prohibit embryo research, with any experiments, and if agreed, only under well-defined conditions»; and *vi)* «urges the swift adoption of strict international control on the release of genetically engineered organisms into the environment» [3].

The Jewish faith holds to the same principles: *i)* «Genetic intervention in "God's creation" is an arrogant human act. Using gene therapy is "playing God" and should not be practised»; *ii)* «The techniques of genetic manipulation can potentially be misused to harm and to damage creation. They, therefore, should not be developed at all» [4].

And finally, as for the Islamic outlook, taking the commandments of the Koran as their basis «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 [...] support a moratorium on genetic engineering and artificial reproduction as applied to man» [5].

But the qualms and misgivings do not only emerge from the religious realm. Hans Martin Sass has described that in Germany, «with the historical antecedent of Naziism and under pressure from strong, so-called "alternative" groups, German scientific policy thought it was important to come to a public agreement on the legal and ethical implications of the application to people of genetic

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[3] Stotts, J.L.: «Protestantism and the Human Genome Project», ibid, pp. 149-150.

[4] Aviv, Haim: «Ethical Attitudes of a Jewish Scientist with Regard to Genetic Intervention», Ibid, p. 139.

[5] Guessous, Azeddine: «Artificial Reproduction: An Islamic Point of View», Ibid, p. 129.

technology» [6]. As a result, «preventive medicine with eugenic aims» is rejected in favour of «specific vigilance in precise areas of use and abuse», such as prenatal diagnosis, employment-related diagnostic testing, civil and criminal law cases, data protection and privacy. The first version of the proposed European Community directive on preventive medicine touched off «a stormy debate in the federal parliament». The following paragraph was particularly controversial: «Preventive medicine seeks to protect individuals from the kinds of illnesses to which they are genetically most vulnerable and, where appropriate, to prevent the transmission of the genetic susceptibilities to the next generation».

The alternative platform, strongly anticapitalist in outlook, prevented the Australian bioethicist Peter Singer from participating in conferences he had been invited to attend in Germany in 1989. «Singer, in one of his books, had discussed active euthanasia of severely defected newborns». The debate gave rise to a *gegen Gen und Repro* campaign and the annual meeting of the German Society for Anthropology and Human Genetics was called off because of threats from alternative groups. Also in 1989 the Bochum Centre for Medical Ethics organized an international workshop, which the local Protestant student union threatened to disrupt, though they eventually accepted the invitation to participate in the discussions. They argued that any discussion of genetics was necessarily a discussion of eugenics, that is, to justify and promote eugenics.

One student spokesperson declared: «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». In his reply to the alternative groups Sass has stated: «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 renouncing communication with those who distrust all established forms of communication and dialogue, who find security in internal emigration and in refusing communication, who prefer violence over dialogue, conflict over communication» [7].

In July 1990 the German Genetic Engineering Act (Gengesetz) took effect, containing five provisions relating to this issue and

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[6] Sass, Hans Martin: «A German Point of View», Ibid, pp. 73 and ff.
[7] Ibid, p. 79.

completing the recommendations which had been made by the government group, assuring protection against the risks and hazards caused by recombinant nucleic acids constructed *in vivo.*

It is also worth pointing out the misgivings produced in the purely academic and doctrinal field. J. David Smith has reminded us of the «lesson of Carrie Buck» [8]. In 1927 a young woman named Carrie Buck was sterilized without her consent. She was the first person submitted to this type of surgery under the authority of a Virginia law. To the defenders of this law she seemed to be the ideal person for testing the law. Her mother was mentally deficient, Carrie was mentally retarded, and her daughter likewise showed signs of feeblemindedness. This demonstration of genetic transmission justified the law's constitutionality, and the Supreme Court so judged in the case which came to be known as Buck v Bell. Delivering the Supreme Court's majority opinion, Justice Oliver Wendell Holmes wrote:

«We have seen more than once that the public welfare may 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 Carrie Buck case was followed by thousands of others. The Virginia law became a model for the laws of other states: a conservative estimate is that 50,000 people were sterilized in the United States. It must also be admitted that this law was the model used by the Nazi racial hygiene programme. On July 14th 1933 the German Sterilization Act was modelled on the Virginia law. It is estimated that between 1933 and 1945, two million people were declared defective and were sterilized by the Nazis. It is curious that when Otto Hoffman, a high ranking SS officer, appeared in the war crimes trial in Nuremberg, his counsel argued his innocence by recalling the doctrine set down by United States Supreme Court Justice Holmes in 1927. Later investigations demonstrated that the evidence which led to Carrie Buck's sterilization was grossly inaccurate. The daughter said to represent «the third generation of imbeciles» grew up to be «an attractive child who was an honour roll student». Carrie was paroled after

[8] Smith, J. David: «Biological Determinism and the Concept of Social Responsibility: The Lesson of Carrie Buck», ibid, pp. 157 and ff.

her sterilization and sent to a mountain village, where she married the deputy sheriff and led a productive and respectable life. Echoing David Smith's conclusion to his account of the case, it is not true that human life can be reduced to biology and that human institutions can be better guided by the realities of biological determinism.

Legal issues: the solution under Spanish law

1. Legal problems to be examined

Throughout the foregoing analysis I have referred to the problems of law raised by biotechnological developments. With a view to the solutions offered under our positive law, I will next study the following:

a) In relation to the «major issues»:

1) Regarding legalization of artificial procreation methods; 2) regulation of gamete and ovocyte donation; 3) the problem of so-called «rented» wombs; 4) the creation of embryo, sperm and ovocyte banks; and 5) the donation and manipulation of embryos and fetuses.

b) The second reflection will take up the specific legal problems arising from the above-described situations: paternity-filiation; public and private employment; insurance contracts; health care and education... Some of these issues are specifically and more fully addressed in other presentations.

c) Lastly, I will address the specific question before us: the defence of personal privacy and the confidentiality principle which should govern genetic manipulation of all types.

Let me begin by reviewing the legislative process by which Spain has legalized many biotechnological techniques.

a) The extraction, transplantation and donation of human organs was already regulated by Act 30 of October 27th 1979. It should be recalled that transplantations have so greatly benefited humanity and saved so many lives that, in general terms, they have never met with any opposition on ethical, moral or religious grounds. On the contrary, such donations have been encouraged, and society has high regard for individuals who volunteer to become donors. Thus, no problems have arisen in this area with regard to the defence of the

right to privacy, although the donor obviously maintains the right to confidentiality in relation to the donation.

Now, the donation of sperms and ovocytes and the extraction and manipulation of embryos and fetuses is a significantly different question. To begin with, Act 35/1988 already opened a dangerous and questionable path when it regulated and permitted several assisted reproduction methods. It was later complemented by Act 42/1988, which attempted the difficult task of adapting these techniques to ethical and social requirements. But let me take this review one step at a time.

1) At present, methods of artificial reproduction (or assisted reproduction as they are termed under the Act) are regulated, and therefore legalized, by Act 35 of November 22nd 1988. This Act, in its statement of purpose, referring to the growing use of these methods, says:

   «Among them, artificial insemination (AI) with semen from the husband or the male member of the couple (CAI) or from a donor (DAI) has been carried out for several years: in Spain, the first semen bank dates back to 1978 and this procedure has led to the birth of some 2,000 children in our nation and several hundred thousand more in the rest of the world. *In vitro* fertilization (IVF) with embryo transfer (ET), technically more involved, became universally known in 1978 with the birth of Louise Brown in the United Kingdom. In our nation, the first of the 50 births hitherto produced by this method took place in 1984. Intra-tubaric gamete transfer (IGT) is beginning to be performed in Spain.

   It is estimated that in Spain there are some 700,000 sterile married couples of fertile age, or around 10 to 13% of the total, of which around 40% could benefit from IVFET or similar methods and some 20% from artificial insemination [...] These are now more than possible alternatives to infertility.

   The availability of ovules from the moment of their *in vitro* fertilization allows the researcher to manipulate them for diagnostic, therapeutic, or basic or experimental research purposes, or for genetic engineering, which are no doubt beneficial to the individual and humanity but, in any event, given the material involved, generate a diaspora of implications that rouse social, ethical, biomedical and legal fears and uncertainty».

   The Act explains the ethical outlook as follows:

«From an ethical standpoint, society's pluralism and divergence of opinions is often seen in connection with the different uses to which assisted reproduction methods are applied. Their acceptance or rejection should be argued from a properly informed outlook and not be motivated by any special interests or ideological interests of a denominational or political nature, but solely grounded in a civic or civil ethics, not devoid of pragmatic components, the validity of which resides in the acceptance of reality once it has been examined with rational criteria at the service of the general interest. An ethics, in short, which echoes the sentiments of the majority and the Constitution can be assumed without social tensions and be useful to the legislator in adopting positions or laws.

Scientific advances generally run ahead of jurisprudence, which trails behind in its accommodation of the consequences of the former. This asynchronism between science and law generates a legal void with respect to certain specific problems which must be solved if individuals and society are not to be rendered defenceless vis-à-vis certain situations. Such legal voids have been created by the new assisted reproduction methods and their implications for administrative, civil and criminal law. All the elements involved in assisted reproduction methods need to be reviewed and evaluated in order to properly adapt the law with respect to: the embryological material employed, the donors of said material, the female subjects of the techniques and the males involved, where such is the case, the offspring, the manipulations which these techniques can produce (ovarian stimulation, cryogenic conservation of gametes and pre-embryos, prenatal diagnosis, basic and experimental gene therapy research, genetic engineering, etc)».

Accordingly, section I of the Act regulates the different assisted reproduction methods enumerated earlier «when they are scientifically and clinically indicated and performed in authorized, accredited scientific and health care centres and establishments by specialized staff». It regards these methods as lawful provided «their fundamental purpose is medical treatment of human sterility, in order to facilitate procreation, when other therapeutic techniques have been discarded as inadequate or ineffective». Paragraph 3 provides:

«These methods may also be used in the prevention and treatment of genetic or hereditary diseases, when their

use offers sufficient diagnostic and therapeutic guarantees and they are strictly indicated.»

«4. Investigation and experimentation with human gametes or fertilized ovules may be authorized under the terms set out in sections 14, 15, 16 and 17 of this Act».

2) The donation of gametes and ovocytes is specifically envisaged in section 5 of the Act:

«1. The donation of gametes and pre-embryos for the purposes authorized under this Act is a *gratuitous, formal and secret contract* made by the donor and the authorized Centre».

3) Conversely, the law does not recognize the legal validity of so-called «rented wombs», which are prohibited pursuant to the principle that child delivery determines maternity. Thus, section 10 of the Act tells us: «Contracts for the gestation, with or without consideration, by a mother waiving maternal filiation in favour of the contracting party or a third party shall be null and void by law»; 2. «The filiation of children born by surrogate gestation shall be determined by the child delivery»; 3. «The right to institute paternity claims with respect to the biological father, in accordance with the general rules therefor, shall be maintained.» The last provision, incidentally, clashes with the secret character of gamete donation.

4) Chapter IV of the Act permits the creation of semen and ovule banks, and rigorously sets down the types of manipulations which are prohibited.

Section 11 provides: «The semen may be cryogenically preserved in authorized gamete banks for a maximum of five years [...] Cryoconservation of ova for use in assisted reproduction shall only be authorized when there are sufficient assurances as to the viability of the ovules after they have been unfrozen».

Section 14 addresses research and experimentation with gametes as well as with live pre-embryos. Fertilization of humans with animal gametes is prohibited, and the conditions are set down under which research can be conducted on live pre-embryos. Deserving particular attention are the serious offences, particularly those envisaged in paragraphs *k)* et seq of section 20.2; for example, the prohibition on creating human beings through any type of cloning procedure, gender selection, or the fusion of pre-embryos to produce «chimeras». Also outlawed is the mixing

of human and animal gametes or pre-embryos. Of course, just the contemplation of these possibilities is chilling.

b) Act 42 of December 28th 1988 on the donation and use of human embryos and fetuses or their cells, tissue or organs, represents another regulatory step in this field. The Act's statement of purpose declares that «the manipulation of or traffic in human embryos and fetuses impels ethical and social reflection and underscores the need for a legal framework for proper regulation of biomedical activities based on respect for life, dignity and human rights, without closing off the path to science, heritage of all humanity».

The principles at work in the Act are the following:

1. The donation and use of human embryos and fetuses (or their cells and tissues) is permitted for diagnostic, therapeutic, research or experimental purposes «under the terms set out by the Act».

2. The embryos and fetuses must be *dead or clinically inviable* (section 2e); the donors must be the progenitors (consent in writing) and cannot be remunerated in respect thereof.

3. Pregnancies cannot be ended for purposes of donation. The medical personnel who have participated in the abortion are barred from any later use of the fetuses or embryos (section 3).

4. Fetuses expelled from the mother by a miscarriage and «considered biologically viable» shall only be treated so as to favour their viability (section 5.3).

5. The extraction of biological structures from dead embryos or fetuses is authorized for the following *permitted genetic technological uses* (sections 6 and 8): *i)* prenatal screening for genetic or hereditary diseases; *ii)* for industrial application to the manufacture of substances having health care or clinical uses; *iii)* for therapeutic purposes, to select gender in cases of diseases linked to the sex chromosomes (especially the X chromosome) and thereby avoid their transmission; *iv)* for purposes of researching and studying human genome DNA sequences.

6. Sections 9 and 32 to 37 of the General Health Act of 1986 specifically prohibit: *i)* alterations of the human «non-pathological» genetic heritage; *ii)* keeping embryos or fetuses alive for purposes other than procreation; *iii)*

donation for cosmetic products; *iv)* extraction of developing embryo or fetus cells or tissues for any reason other than prenatal diagnosis.

7. The donation and use of fertilized gametes and ovules *(in vivo* or *in vitro)* until day 14 from their fertilization shall be done under the terms of Act 35/88 on assisted reproduction.

If I were asked to give an overall opinion on our positive legal provisions, I would have to say that it certainly places few obstacles in the path of genetic research; the limitations contained in the Act constitute the law's ethical minimum. To eliminate such limitations (say, to assay human animal hybrids) would constitute an obscene affront to the Creation or to the laws of Nature, depending on the terminology preferred by each person. Someone has claimed (and I don't dare label him an optimist) that genetic research will demonstrate the essential equality of all races. But what if it were to demonstrate the contrary? It would be the great scientific triumph of racism. It would no longer be necessary to resort to twisted interpretations of the Sacred Scriptures (as was done in the past by supporters of slavery) in order to impose eugenic laws or new forms of slavery. This is why there are some questions in which legislation must not trail behind science. The example of Galileo should not serve to impose the opposite principle of «prohibitions prohibited».

2. *Secondary legal problems*

The legislation examined above, and the human genome project in general, pose numerous derivative legal problems. I will confine myself here to suggesting the following:

a) The first –and this is a current not a future problem– refers to the paternity-filiation relation, which obviously becomes more complicated where fertilization is allowed with gametes from anonymous donors.

The aforecited Act 35/1988 regulates this area. Section 6 refers to the female who uses these methods, and whose informed consent is required. «If she is married, the consent of the husband is also required [...] unless they are separated by a final divorce or separation judgement, or in fact or by a certifiably recorded mutual agreement». Paragraph 5 thereunder provides that «the choice of the donor is responsibility of the medical staff which applies the assisted reproduction technique».

Section 7 refers to paternity and filiation. «The filiation of newborns [...] shall be regulated by the applicable legal provisions except for the special cases contained in this chapter [...] In no event shall the record filed with the Civil Registry include data allowing the nature of the generation to be inferred».

Section 8: 1. «When they have given their consent neither the husband nor the wife shall be able to challenge the matrimonial filiation of the child born as a result of such fecundation».

Section 5, for its part, regulates the right of the offspring in the following terms:

«The children have the right to obtain or have their legal representatives obtain general non-identifying information on the donors. Recipients of the gametes shall have the same right.

The donor's identity can be disclosed only exceptionally, in extraordinary circumstances involving verified danger to the life of the child, or when appropriate in accordance with the rules of criminal justice procedure, provided that such disclosure is indispensable for avoiding the danger or for achieving the proposed legal purpose. In such cases, the provisions of section 8, para. 3 shall apply. Said disclosure shall be limited and in no case imply publication of the donor's identity».

b) The real possibility of attaining a genetic map inevitably opens the door to discriminatory situations, emphatically prohibited by article 14 of our Constitution yet so difficult to avoid. It is quite common to require a person to obtain medical certification that he or she is free of and not excessively at risk from certain diseases in order to qualify for many public employee positions or jobs in the private sector. In the field of life insurance contracts, this practice is the general rule. Of course, no one is obliged –nor perhaps could they be– to reveal the diseases or physical deficiencies they suffer; but could the other contracting party be obliged not to require such disclosure? This is a particularly intricate question when dealing with matrimonies or couples: is it possible to deny the right of one member of the couple to request –prior to establishing the relation– that the other reveal his or her state of health? Indeed, couldn't it be considered as even a criminal offence for someone to conceal a disease such as AIDS from their future spouse?

As we will soon see, not even the right to defend one's privacy can constitute a reliable barrier against this type of discrimination. The Spanish Constitutional Court, in its Judgement number 20 of February 14th 1992, decided in favour of individuals who lodged an appeal for legal protection of their rights under the Constitution after a certain publication had identified them as having AIDS. Notwithstanding the publication's right to inform and to freely express itself, the Court found that the report «occasioned moral (and also economic) damages to the persons who had been so identified as affected by AIDS». But the previous question still stands: who can deny the right of other persons to be adequately informed in order to protect themselves from possible infection?

3. *Privacy rights and confidentiality*

a) Without a doubt the greatest threat to personal privacy comes from the possible enactment of laws that make genetic screening obligatory. What is more, I think what is under attack in this case is the very core of individual freedom.

In 1962, after Dr R. Guthrie's work, some US state legislatures promoted genetic research programmes and in 1963 the state of Massachusetts enacted a law making genetic testing mandatory. By the end of 1965 most states had passed laws of this type, and in the early 1970s genetic screening became particularly extensive in relation to the Tay-Sachs disease (a degenerative neurological disorder). When the US Congress approved the 1976 law regulating subsidies to programmes on genetic diseases, it made funding conditional on such programmes being voluntary.

The potential consequences for the human genome project of these precedents are worrisome. Who will be normal or abnormal if molecular genetics –as scientists are telling us– demonstrates that the difference between disease and non-disease consists solely in the re-ordering of a single DNA base-pair out of the billions contained in each cell? To what new forms of discrimination will this lead?

With some optimism I believe that statutes of this type have no place in Spain's positive law and that if enacted they would be declared unconstitutional. Article 18.1 of the Spanish Constitution provides: «The right to honour, to *personal and family privacy* and to personal reputation is guaranteed.» I think this is the defensive dyke against such laws.

This Constitutional guarantee was implemented by Organic Act 1 of May 5th 1982 on the right to honour, personal and family privacy and to personal reputation. Section 1.1 of the

Act states that this right «shall be protected civilly against any kind of illegitimate intrusion, in accordance with the provisions of this organic act». And 1.2 provides that «when the intrusion constitutes a criminal offence, the provisions of the Criminal Code shall apply. Nonetheless, the criteria of this act shall be applicable to the determination of the civil liability arising in respect of the offence».

Section 7 states that «the following shall be considered to be illegitimate intrusions in the sphere or protection delimited by section 2 of this Act: 1) the dispatch to any site of listening, filming, or optical devices or any other medium for recording or replaying the private life of any person. 2) The use of listening, optical devices...».

For its part, section 2.5 of the above-commented Act 35/1988 provides:

«All data concerning the use of these techniques shall be recorded in individual clinical records, which must be treated with the requisite confidentiality *and in strict secrecy as to the identity of the donors, the sterility of the users, and of the circumstances relevant to the origin of the children thus born*».

b) Article 18.4 of the Constitution declares: «The law shall restrict the use of data processing in order to guarantee the honour and personal and family privacy of citizens and the full exercise of their rights». This precept was implemented by Organic Act 5 of October 29th 1992, regulating the automated processing of personal information. The Act's statement of purpose contains the following declaration:

«The progressive development of techniques for collecting, gathering and accessing data in effect poses a potential and hitherto unknown danger to *privacy*. Note that *it is privacy not intimacy which is under discussion here* [9]: the former is broader than the latter, for intimacy protects the sphere in which the most singularly reserved aspects of a person's life develop –the home in which he lives out his or her daily life, communications expressing his or her sentiments, for example– whereas privacy constitutes a wider, more general grouping of aspects of his or her personality which considered separately could lack an intrinsic significance, but when coherently interrelated render a profile of the individual's personality,

[9] Translator's note: In this passage, a distinction is made between *intimidad* («intimacy») and *privacidad* (privacy). In Spanish law and in the Spanish Constitution privacy rights are usually referred to as «el derecho a la intimidad», literally, «the right to intimacy». In this passage, and this passage only, *intimidad* is translated as «intimacy» and *privacidad* as «privacy».

which the individual has a right to keep reserved. And while intimacy in the strict sense is sufficiently protected by the provisions of the first three para. of article 18 of the Constitution and by the laws which implement said provisions, privacy could be impaired by the use of recent data processing technologies».

The statement of purpose later goes on to say:

«The most varied data –about a person's childhood, academic, professional or work life, living and consumer habits, use of so-called plastic money, personal relations, or even religious beliefs, to cite but a few examples, may be easily compiled and obtained. This would permit anyone possessing such data to acquire information about aptitudes, facts or behavioral patterns that doubtless belong to a person's private sphere; to that sphere which only the individual should have access, along perhaps with those closest to or authorized by him or her. Moreover, an organized knowledge of such data could serve to profile the person or shape a certain reputation or renown, which, in short, is an expression of the person's honour; and this profile could no doubt later be judged, favourably or unfavourably, in connection with a wide variety of public or private activities, such as acquiring employment, being extended credit or admission into determined groups».

Pursuant to these concerns, section 1 states the purpose of the Act: «this Organic Act, in implementation of the provisions of paragraph number 4 of article 18 of the Constitution, has as its purpose to limit the use of computer and other techniques and methods for the automated processing of data of a personal nature in order to guarantee the honour, personal and family privacy of natural persons and the full exercise of their rights». The scope of the Act's application is set down in section 2: «data of a personal nature contained on automated records in the public and private sectors and to subsequent use of any kind, including automated and non-automated uses, of data of a personal nature recorded on physical media apt for automated processing». The cases in which the provisions of the Act are not applicable are then defined (in relation to determined records and other records regulated by specific legislation, such as electoral records and those at the civil registry and the central criminal records registry, etc).

Section 4 provides that «data of a personal nature may only be collected [...] when such data are appropriate, relevant and not excessive in relation to the scope and legitimate

purposes for which they were obtained». This information is to be erased when it is no longer necessary or relevant to the purpose for which it was collected and recorded.

Section 5 establishes the right to information in the collection of data: prior to providing his or her personal data the person is to be specifically informed as to the existence of an automated record, the obligatory or optional nature of his or her reply, the consequences of furnishing or of declining to provide the data, the possibility of exercising the right to correct and cancel the data, and the identity and address of the person responsible for the record.

Section 6 sets down the principle of «the consent of the affected party, which shall be the general rule except where otherwise provided by law [...] Consent shall not be required when the personal data are collected from publicly available sources, when they are collected in the exercise of functions of government agencies [...] nor when they refer to persons associated by reason of a business, employment or administrative relation or by contract and they are needed for the maintenance of the relations or the performance of the contract» (section 6.2).

In accordance with section 7, special protection shall apply to data regarding «declarations as to one's ideology, religion or creed», and the right of the person not to furnish such declaration is recognized. Personal data disclosing an individual's ideology, religion or creed can only be subjected to automated processing upon the express written consent of the individual. «Data of a personal nature which make reference to racial origin, *health*, or sex life shall be collected, processed and transferred solely for reasons of the general public interest, when so provided by law, or when the person gives his or her express consent» (section 7.3). Further reference to health data is made in section 8:

«Without prejudice to the provisions of section 11 concerning transfer, public and private centres and institutions and their respective professional staff may process personal data concerning the health of the persons who consult them, or who are to be treated by them, in accordance with the provision of sections 8, 10, 23 and 61 of the General Health Act (Act no. 14 of April 25 1986), sections 85.5, 96 and 98 of the Medications Act (Act no. 25 of December 20th 1990), sections 2, 3 and 4 of Organic Act no. 3 of April 14th 1986 on special measures in matters of public health, and other health care legislation».

Transfer of data: «Data of a personal nature [...] shall only be transferred in the course of fulfilling the aims directly related to the legitimate functions of the transferor and transferee and with the prior consent of the interested party» (section 11.1). And para. 2f of that same section 11 adds: «When the transfer of personal *health-related* data is necessary for the solution of an emergency that requires accessing an automated data record or for conducting epidemiological studies under the terms of section 8 of the General Health Act (Act no. 14 of April 25th 1986)» (in which case the consent of the interested party shall not be required).

Title III of the Act sets forth the following rights: 1) to challenge evaluations based solely on automated data (section 12); 2) to obtain information (section 13); 3) to have access (section 14); 4) to correct and cancel (section 15). The protection of these rights and the right to compensation are regulated by section 17 of the Act.

In a systematic study of the law, professor Murillo de la Cueva, employing dubious terminology, has spoken of the «right to informational self-determination» [10]. But certainly the term applied is the least of it; what is important is to ascertain whether there is a genuine legal protection that assures the individual as to the handling of his or her personal and private data, made so vulnerable nowadays by information technologies. For we find ourselves at a critical juncture where the alliance between biotechnology and information technology could bring about –deliberately or by the sheer momentum of its development– the annulment of the very core of human personality [11].

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[10] Murillo de la Cueva, PL: «La protección de los datos personales ante el uso de la informática en el Derecho español» [The protection of personal data and the use of information technologies under Spanish law], *Estudios de Jurisprudencia. Revista Colex*, no. 4, January-February 1993, pp. 7 and ff.

[11] Obviously, our Constitutional Court has thus far not had an opportunity to pronounce itself on the protection of a person's genetic data, nor, for that matter, as far as I know, on computer invasions of privacy. There is, however, abundant case-law containing judgements as to the clash between the «right to privacy» and the «right to freely communicate or receive accurate information» (articles 18 and 20 of the Spanish Constitution). Given below is a sampling of the Spanish Constitutional Court's judgements in this area:

i) Judgement of the Constitutional Court no. 231 of December 2nd 1988, responding to an appeal for legal protection of constitutional rights in connection with the images that were published and broadcast of the death of the bullfighter Francisco «Paquirri» Rivera: «With respect to the first, they are from the moment when Mr. Francisco Rivera was brought into the medical care unit and examined by the doctors. The images clearly and directly show the wounds suffered, the situation and reaction of the injured man, and his emotional state, which is revealed in the images of his gestures and face, and which certainly demonstrate the matador's composure, but also the pain

and prostration caused by the wounds. Thus, it can certainly be inferred, within the context of our cultural mores, that they have a negative impact, causing pain and anguish to the deceased's closest relations, not only because of the situation they reflect at that moment, but also when linked to the fact that the wounds and injuries shown there caused the bullfighter's death shortly thereafter. Hence, there can be no doubt that the images in question, according to the foregoing, affect the personal and family privacy of the person bringing the application before this Court, at the time the wife and now the widow of the departed Mr Rivera» (sixth fundamental point of law of the judgement).

i) Constitutional Court Judgement no. 110 of November 26th 1984, responding to an appeal for legal protection of constitutional rights in connection with a finance ministry investigation of bank current accounts: «Explicit constitutional recognition of the right to privacy is a recent development and found in very few Constitutions, Spain's among them. But its underlying idea, the respect for private life, is present in some of the traditional liberties. The inviolability of a person's home and correspondence, to name some of these traditional liberties, has as its prime aim to guarantee respect for the private sphere of persons and families, which sphere must be closed off to inquiry and intrusion by anyone not having the consent of the interested persons. What has occurred is that modern-day technological advances and the growth of the mass media require that this protection be extended beyond the defence of the home, as the physical space in which a person leads his private life, and of correspondence, as a medium which can be potentially used to discover aspects of a person's private life. Hence the general recognition of a right to privacy or to private life that covers intrusions made by whatever means in that reserved realm. It is not always easy, however, to clearly delimit the boundaries of privacy» (third fundamental point of law of the judgement). «The first problem posed by the present case is to determine the extent to which data concerning a person's economic situation and difficulties qualifies as lying within the constitutionally protected private sphere. In the present case the question arises with respect to the government and can be stated as follows: to what extent can the government demand data as to a taxpayer's economic situation? No doubt, the government, in principle, has such right. The mere fact of the tax system's existence and the oversight and verification activities required for its effective function so demonstrate».

iii) Constitutional Court Judgement no. 20 of February 14th 1992, responding to an appeal for legal protection of constitutional rights in connection with news publication of a person's AIDS infection: «The question of whether or not the news report was true in this case is not crucial to the resolution of this appeal, for the privacy safeguarded by the Spanish Constitution is made no less worthy of protection by the veracity of information concerning "the private or family life and affecting their reputation and good name" (section 7.3 of Organic Act 1/1982). Freedom of information is a right with respect to which the Spanish Constitution dispense maximum protection, and its exercise is linked to the objective value of free public communication. But when said freedom is exercised in areas which can affect other constitutionally protected principles, such as honour and, in this case, privacy, *the reported news must be of public interest for its dissemination to be legitimate*. In the present case privacy was transgressed; for in no way can anybody be forced to passively tolerate media broadcast of information, true or supposed, about their private lives which affects their reputation, according to the common sentiment, and which is indifferent or trivial to the public interest. The indirect but unmistakable journalistic identification of a certain person affected by AIDS occasioned pain and suffering (and economic damages) to those who found themselves thus singled out as AIDS victims. And it is also patently obvious that the identification of persons supposedly affected by the said disease was irrelevant to the information being reported».

iv) Constitutional Court Judgement no. 227 of December 14th 1992, responding to an appeal for court protection of constitutional rights in connection with publication of a press notice disclosing the assessment of an admi-

nistrative sanction: «As occurs in all cases where there arises *prima facie* a clash between the rights set down in article 18 and those in article 20 of the Constitution, it is incumbent upon the trier to identify, where such is the case, the right which has been violated, by a process of weighing the concrete circumstances of the case (in this sense, *inter alia*, Constitutional Court Judgements 105/1990, 171/1990 and 172/1990). In particular, as the case involves the right to communicate information, the circumstances relevant to this process are the subject matter of the information, its public interest, its capacity to contribute to the formation of a free public opinion, the public or private nature of the reported person, and the information medium, that is, if the information was disseminated via the mass media. If the finding contained in the Judgement of the First Chamber of the Supreme Court were correct, that is, if we are in fact before one of the cases provided for in section 7.4 of Organic Act 1/1982 (illegitimate intrusion produced by the «disclosure of a person or family's private information obtained in the course of the disclosing person's professional or official activity»), the conclusion must be a judgement against the present appeal for court protection of constitutional rights, for the right to freely communicate accurate information does not extend to the disclosure of a person or family's private information obtained in the course of a professional or official activity. Conversely, if the above were not the case (contrary to the finding on which the Judgement under appeal was based), the equally necessary conclusion must be a judgement in favour of the complaint, with the attendant declaration that the right to communicate information had been infringed. In the case at bar, the disclosure of the sanction to the press by the appellant cannot be deemed to be «private information» within the meaning of section 7.4 of Organic Act 1/1982. Irrespective of the fact that the assessment per se of disciplinary sanctions or penalties does not infringe the right to honour *(inter alia* Constitutional Court Judgement 50/1983), the press publication thereof cannot, in this case, be considered as the disclosure of private information». Lastly, for more on the conflict between the right to information and the «right to honour» (so linked to privacy), see González Pérez, J: *La degradación del derecho al honor (honor y libertad de información)*, Civitas, Madrid, 1993.

RIGHT TO CONFIDENTIALITY: USE OF GENETIC INFORMATION

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There is broad agreement about the importance of protecting the privacy of genetic information about individuals. But the speakers on «Right to privacy: use of genetic information» demonstrated that legal regimes will not easily, and certainly not uniformly, define and implement the protection of genetic privacy. Many of the speakers observed that an individual's right to privacy is not absolute but must yield under certain conditions to the claims of other individuals or the public at large. Other speakers emphasized the predominance of the individual's right to privacy. The need to balance conflicting claims to genetic information about individuals will challange those seeking to develop legal standards in this area, and a variety of resolutions in different political settings can be anticipated.

The efforts of the Council of Europe and the Commission of the European Communities to protect privacy generally, and genetic data specifically, have not resulted in wide agreement on the extent of protection that should be provided. The broad principles regarding privacy that have been adopted or are being considered by these international organizations permit a variety of

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interpretations and, further, leave many important decisions to national legislation. This latitude recognizes the different traditions and approaches of different cultures and countries. However, the potential exceptions left to national decision making could significantly reduce protection from disclosure or missuse of individuals' genetic data in some jurisdictions.

In the United States, legislation on matters such as privacy is usually the last resort. Legal protection may instead be generated from the bottom up, through litigation of cases. Coverage of a new area such as genetic privacy may develop by analogy from existing case law. Cases in which recovery has been granted against physicians for failure to warn couples that their offspring might inherit a genetic disorder, against sexual partners for failure to disclose a sexually transmitted disease, and against a patient for failure to disclose to his physician that he was HIV positive may indicate a trend toward requiring individuals to disclose information about their genetic condition to their spouses or prospective spouses, even if the individuals themselves do not wish to know such information.

As the countries of the world develop various means of protecting genetic information from disclosure or misuse, factual understanding of the values and uses attached to such information should inform the application of governing principles. Perhaps the diversity of legal responses during the initial period will enable a useful comparison of approaches in the future.

Programm on the ethical, legal and social aspects of the Human Genome Project. United State Department of Energy. Description of the state of the investigation as of May 1st 1993.

Philosophy

1. Powers

«The Right of Privacy Reconsidered» (commissioned paper, draft 1993).

Descriptive account of privacy from the perspective of philosophical analysis, with application to the challenges to privacy raised by the collection, storage and dissemination of genetic information.

Provides a typology of contexts in which privacy issues related to genetic information may arise and public policies that may be appropriate in each context.

Rights to privacy (limiting others' access to personal information) are contingent upon the interests at stake in different contexts.

Interests at stake
a) Life prospects, e.g., employment, insurance.
b) Autonomy, e.g., reproductive choice.
c) Intimacy, e.g., familial relations.
d) Social standing, e.g., stigma.
e) Self-concept, as affected by information about oneself.

Further complication
a) Probabilistic and variable nature of genetic information.

Types of privacy rights
a) Control the generation of information.
b) Control the disclosure of information.
c) Non-control rights.

Scope of privacy rights
a) Privacy interests are not absolute but must be balanced against collective good.
b) Making privacy less important may be preferable to protecting privacy in some instances, for example, reform U.S. health insurance.

Social science

1. Westin

«Social Science Concepts and Sutdies of Privacy: A Comprehensive Inventory and Analysis for Use in Consideration of Privacy, Confidentiality and Access Issues in the Use of Genetic Tests and Applications of Genetic Data» (grant commencing 1993).

Review the social science theoretical and empirical work on privacy since Westin's *Privacy and Freedom* (1967), refine the concepts and operative dynamics first formulated by Westin in light of research and social developments since 1967, and relate this updated research and reconceptualization to the privacy, confidentiality and access issues likely to arise in connection with genetic data, including genetic databanks.

Also, examine the development, implementation and effectiveness of current legal and organizational privacy protection measures in the US, current debates over the updating of privacy protections to reflect new scientific, technological, social and cultural

changes, and the implications of our experience with privacy protection and the current privacy debates for choices of social, organizational and legal policies to deal with the expected genetic testing and data applications of the future.

2. Duster

«Pathways to Genetic Screening: Patient Knowledges-Patient Practices» (grant comenced 1992).

Empirical study to clarify the cultural frames used to process new genetic information and to explore both barriers and bridges to successful genetic intervention.

Project will reach beyond the clinic into high-risk groups of young men and women in their early reproductive years who have not yet taken advantage of screening options.

Compare those who have used genetic services and those who have not yet done so.

Examine social networks and extended family members of those whose lives have been touched by the targeted genetic disorders, focusing on the issues of privacy, stigma and discrimination, and their management within family and institutional networks.

Analyze the understandings, interest and responses in two cultural contexts, one in which the disorder is generally recognized as race-linked and the other in which this association is not part of the popular consciusness.

3. Trottier

«The Impact of HGI-Derived Technologies on Genetic Testing, Screening and Counseling: Social, Ethical and Legal Issues» (grant commenced 1992).

Empirical research to examine ethical and social facets of two legislatively mandated genetic screening, testing and counseling programs (Georgia and Florida), with particular scrutiny of how various urban and rural ethnic groups are currently served by these programs.

Explore question of when confidentiality of genetic information should be breached for a prevailing interest that supersedes privacy interests of the affected individual(s), in several contexts: relatives, spouses or potential spouses, parents or prospective adoptive parents, adopted children, judicial proceedings for dis-

covery of medical records, insurers, researchers, schoools, employers.

4. Barash

«Studies of Genetic Discrimination» (gran commenced 1992).

Empirical study to assess the significance of genetic discrimination in the US.

Goals

a) Determine the particular social institutions that might engage in discriminatory practices, such as insurance companies, governmental agencies, employers, educational institutions and the military.

b) Evaluate the nature of the discrimination experienced by individuals dealing with these institutions and agencies, and determine the underlying basis of the discrimination.

Methodology

a) Case history analysis, employing a survey of persons with well-documented single-gene disorders, persons at risk for certain single-gene disorders, and asymptomatic heterozygotes for other conditions, with detailed follow-up interviews when apropriate.

Law (US)

1. Reilly

A) *«Genetic Data and Privacy»* (grant commenced 1991).

1. «State Legislative Efforts to Regulate Use and Potential Misuse of Genetic Information», *Am. J. Hum. Genet.* 51(3): 637-647 (1992).

Conclusions

a) State legislative activity regarding genetic confidentiality, informed consent, and discrimination is increasing, particularly in the areas of employment and insurance; there are few legal impediments to prevent genetic discrimination in other areas.

b) But there are still major gaps in coverage that can only be addressed by comprehensive genetic privacy and discrimination legislation.

c) Deficiencies:
- Many bills and statutes fail to define «genetic» or «hereditary» with sufficient breadth.
- Most genetic-specific laws do not clearly distinguisn between carriers and those who actually experience manifestations of genetic disease.

d) Confidentiality:
- Most statutes addressing confidentiality say little more than that the information gathered in state genetic screening programs for specific traits shall remain «confidential».
- Most statutes are silent about such issues as conditions for disclosure of genetic information to relatives and procedures for waiving consent to release of genetic test results.
- Few statutes establish penalties for confidentiality violations or establish any detailed enforcement mechanism.

e) Key elementos that should be covered in legislation:
- Recognize that unauthorized disclosure of genetic information may seriously harm individuals and their families.
- Define who should be authorized to collect genetic information and under what circunstances.
- Specify how genetic information should be stored and who should control access to it.
- Permit qualified researchers with legitimate protocols to have access to anonymous genetic information.
- Subject individuals to civil liability for knowingly or negligently, and to criminal penalties for knowingly, disclosing genetic information without proper authorization.

2. *«A Survey of State Insurance Commissioners Concerning Genetic Testing and Life Insurance», Am. J. Hum. Genet.* 51(4): 785-792 (1992).

Findings
There is considerable uncertainty among state insurance commissioners regarding the use of genetic information.

Life insurance companies have a wide latitude under state regulation to make use of genetic information, if they wish to do so.

Life insurance regulators do not perceive that genetic testing currently poses a significant problem in how insurers rate applicants or that consumers currently are filing complaints about the use of such data in underwriting.

«A Survey of Medical Directors of Life Insurance Companies Concerning Use of Genetic Information», Am. J. Hum. Genet. (in press).

Results
Few life insurance companies perform genetic tests on applicants, but most are interested in accessing genetic test information about applicants that already exists.

The degree of life insurers' interest in using genetic test results may depend on the face amount of the policy applied for and the specificity and sensitivity of the test in question.

Many companies employ underwriting guidelines regarding genetic conditions but do not always have detailed actuarial data on those conditions to support rating decisions.

Most insurers' rating decisions involve a considerable degree of subjectivity.

Some medical directors are not fully informed about certain basic principles of medical genetics.

B) *«DNA Banking and DNA Databanking: Legal, Ethical and Public Policy Issues»* (grant commencing 1993).

Empirical research

Methodology
Review relevant state and federal laws and regulations.
Conduct survey on the operation of forensic, academic and commercial DNA banks.
Site visit two forensic DNA banks, two academically based DNA banks, and two commercial DNA banks, and conduct interviews concerning mechanisms to protect security of samples and data. Also study military's DNA collection effort.

Objectives
Learn how those involved in various types of DNA databanking handle informational privacy, paying special attention to technical issues of computer security. Analyze current approaches. Suggest guidelines for the future.

Education
Produce and distribute half-hour documentary video, with accompanying written materials, about technological, legal, ethical, and public policy concerns surrounding DINA databanking.

2. *Annas*

«Guidelines for Protecting Privacy of Information Stored in Genetic Data Banks» (grant commencing 1993).

Legal reserch project to develop proposed policies and laws to safeguard personal genomic information stored in genetic data banks, by answering these questions:

a) How is genetic information like and unlike medical information?
b) Under what circumstances should it be legally permissible for private entities or public agencies to obtain DNA samples from individuals?
c) When is consent required for storage of DNA samples and genomic information, and can it be given when the meaning of this information is unknowable?
d) Who owns genomic information? Does a genetic databank have a duty to notify individuals of new information that can be obtained from their stored genetic data, or to notify relatives that they have, or are at risk for developing, a serious condition?
e) Who can have access to stored DNA and genetic information, and for what purposes? Should the individual have access to and/or the right to destroy it, and under what circumstances?
f) Should there be time limits for DNA and genetic information storage, and, if so, how should such limits be set?

Colaborate with Reilly, *supra*.

3. *Andrews*

«The Legal and Moral Wight of Genetic Bonds: Privacy, Responsibility and Family» (commissioned paper due 1993).

Multidisciplinary investigation wherther genetic bonds create responsibility to disclose genetic information to relatives, by exploring:

a) Responsibilities relatives are thought to have for each other.
b) Whether responsibilities and rights that hinge on genetic relationship are expanding or contracting.
c) Underlying rationales for giving legal and moral weight to genetic bonds in assignment of rights and responsibilities, from the philosophical, anthropological and historical literatures on the family, and legal sources.

Questions to be addressed:
a) Should parents have access to children's genetic information, and vice versa?
b) Should other at-risk relatives have access to patients' genetic information?

c) What effect should adoption have on any rights or responsabilities in this area?
e) Should spouses have access to their spouses' genetic information?
f) Should it be possible to comple a relative's participation in linkage studies?
g) Should the notion of «patient» in the genetic setting be interpreted to mean «family»?

4. *Grad*

«Lawful Uses of Knowledge from the Human Genome Project» (grant commenced 1992).

Examine the rationale for the protection of genetic information, balancing legal protection for confidentiality against the values of disclosure for the protection of the public or some of its members, and weighing the risk of discrimination against the risk of failure to disclose to spouses or intended spouses and the appropriate government agencies that need information for sound policy purposes.

Study the availability of genomic infomation and the need to collect such information for public health planning, plannning, therapeutic services, and program development.

Foreign and international

1. *Knoppers*

«Privacy and Genetic Information: A Comparative Approach» (commissioned paper due 1993).

Comparative survey of personal data protection.

a) International texts.
b) Civil and common law countries.

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PAPERS

IS THERE A LEGAL DUTY TO DISCLOSE GENETIC CHARACTERISTICS TO A FUTURE SPOUSE

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Much of the literature on the dangers of genetic knowledge focuses on the risks to employment opportunities and questions of insurance. I have always been more captured by a different set of problems: problems of personal obligation, both moral and legal.

My question here is whether an individual has a duty to tell a spouse or a prospective spouse about his genes, if their future children will be at risk for a serious genetic disease? Must he tell if he is himself at risk for a late onset disease? Does it matter whether he knows for sure, or simply knows the possibilities based on his family history? If others know his condition, may they tell? If silence is wrong, what kinds of remedies are possible? Are these issues of private morality only, or can we envision framing legal rules about them? Should regulation, if it is to occur, come from legislatures rather than from courts?

The legal obligation to disclose is in some flux in American law. In that respect my attention was recently attracted by a California case that was widely reported in the United States tabloids. Ronald Askew was awarded $242,000 from property otherwise

due his spouse in a divorce because she had *not* told him, prior to marriage, that she did not find him sexually attractive. Despite her knowledge during their pre-nuptial period that «openness» and «honesty» were central values of his, she misled him, and he discovered the truth only during a marital counselling session when she recounted that she loved him but did not think him sexy.

We do not know whether this California decision will be a beacon or an oddity, because, like theatrical productions, cases have their trial runs.

The «common law» system as administered in the 50 individual United States tests whether legal variation can survive because it welcomes so many cases. The courts apply core rules of personal obligation that are phrased in the most general language. The judges are not professionally trained as such, and are bound to no accepted theory of the limits of legal change. If the rules are framed in general terms –such as «what is reasonable in the circumstances»– the juries make many of the ultimate decisions. And juries are simply ordinary citizens assembled for the single occasion. The potential recoveries to be had are huge. It often costs the plaintiff next-to-nothing to try, for access to the court is cheap. Lawyers take risks because contingent fees promise them as much as 40% of the recovery.

I shall spare you most of the biological metaphors. Can you imagine, however, any medium better suited for growing lawsuits, and more likely to test whether legal ideas are ready yet for their time in the sun? Such a system produces legal change at such a high rate that the groundwork can be laid for legal transformation almost without notice. Moreover, precisely because the United States' litigation system is so dynamic, its legislative practices are conservative ones. The preference is to let courts work through problems, before legislative action is tried.

Despite our plethora of judicial decisions, so far as I am aware, no reported decision treats the duty to make genetic disclosures in the marriage context. Nonetheless, so many other American legal developments point this way that the first test case cannot be far away. Let me note the principal trends.

1. A number of decisions have held actionable medical failure to alert a couple to the desirability of genetic testing in their particular situation, and some recognize the parent's grief and financial hardship in raising a child they might otherwise have aborted as a cognizable harm. *Schroeder v. Perkel,* 87 N.S. 53, 433 A.2d 834. If this failure to warn adequately is actionable when the physician fails to warn, is it not probable that the

same «harm» must be considered actionable no matter by whom it is «caused». The focus, in other words, must be on the nature of the duty, not on whether the birth of a child is somehow beyond the law's categories of legally cognizable harm.

2. A now substantial body of law exists holding it actionable for a person with a sexually transmissible disease to have sexual intercourse without disclosing that fact, at least when the disease was in fact transmitted. *Berner v. Caldwell,* 543 So.2d 686 (Ala. 1989) (herpes). Moreover, there are a number of American jurisdictions where *fear* of AIDS, and hence exposure to HIV, is held to be a compensable emotional injury. In California, there has been the first decision of which I am aware holding a *patient* liable for failing to disclose to his surgical team that he was HIV positive. *Boulais v. Lustig,* Ca. Sup.Ct. No. BC-038105. Inasmuch as the risk of condom failure is likely as high as the probability of transmission in an operating room, is it the case that an HIV positive person cannot lawfully have sexual relations with anyone without disclosure? If so, what does this do to the likely circle of partners? Is it any wonder that the journals of the night print so many advertisements saying «HIV positive seeking same».

   The HIV examples involve disease, and the disease status of genetic variations is, of course, one of the great ethical and policy fights in genetics. Moreover, the spousal duty to disclose involves, at bottom, future lives and lifestyle rather than present personal injury. Are those sufficient distinctions?

3. The American women's movement has been very successful in forcing reconceptualization of the law of sexual assaults. In order to free the law of anachronisms such as the victim's obligation to resist a rape effort to her death, rape has been redefined as having sexual intercourse without consent. Once force is removed as a necessary element, and consent becomes key, can the notion of informed consent be far behind? In recent years there has been a federal fraud prosecution of a man who misrepresented himself as having contacts in the movie business to secure sexual relations, and there have been successful suits for damages by women who have become pregnant despite assurances by their partners that they were infertile. *Alice D. v. William M.,* 450 N.Y.S.2d 350 (Civil Ct. 1982). The March issue of the *Columbia Law Review,* our Law School's publication, includes an article provocatively titled «Women Understand So Little, They Call My Good Nature "Deceit": A Feminist Rethinking of Seduction» (pp. 374-472). It argues for expanded tort remedies for sexual fraud.

4. The traditional American family as an institution is under sharp pressure these days, as fewer and fewer people live in such arrangements. Inevitably, it seems to me, this creates pressure to expand legal concepts of family by adapting family law rules to family-like relationships created by consent. In making consent the key, however, traditional contract notions of fraud in the inducement and duties to disclose come to the fore.

   It might, of course, be possible to distinguish exchanges of genetic information from these trends, or at least to say that no affirmative obligation exists to disclose, only a duty not to lie if asked. And any partner who asks about the future me, or more properly thinks of the future me in genetic terms, is so hopelessly unromantic that to ask the question is to reject the relationship. After all, our present courtship rituals do not usually include a sharing of family medical histories, and are not they as likely predictive as most genetic information may be? Perhaps so, but social practice is, I believe, contingent on what kinds of information the culture values. The uses of genetic information will spread. If my medical records and genetic characteristics are on a chip embedded in a plastic card, the better to guide my physicians in ascertaining whether a particular drug is contraindicated for persons like me, will it be too long before computer programmers develop algorithms to predict whether you and I are a suitable match? I think not.

TOWARDS GENETIC PRIVACY

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The gradual evolution of the interpretation of privacy from a notion of property and protection to that of liberty and promotion, has been accompanied in the last decade by legislation governing privacy and access of personal and medical data but not genetic information *per se*. Like the concept of privacy itself, the notion of genetic information is indeterminate in nature and controversial as to its legal qualification. While the field of data protection has fostered the theory of informational self-determination, the true locus of the realisation (if not expansion) of this theory in the field of human genetics requires an understanding of the polymorphic nature of genetic information (I). Traditional individualistic concepts of privacy as freedom in, and protection of, personal relationships, of physical integrity and as just mentioned, of personal information from interference must now be weighed in the context of human genetics at the personal, familial and social levels. Public interest and private relations are no longer inseparable in the search for the foundations of a new «infogenic ethics» (II). Thus, only an integrated approach to the protection and circulation of genetic information can serve as the basis for the recognition of genetic privacy.

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* Le Bries, S. and B. M. Knoppers, *Privacy and Genetic Information: A Comparative Trilogy*, DOE Grant, forthcoming, 1993.

The «tryptic-dyptic» nature of genetic «intimacy»

Genetic information is by nature, individual, familial and universal. In its composition, it incorporates the identity, individuality and integrity of the person. These three levels correspond to certain mechanisms of social organization found in the animal species where personal distance is the necessary territorial space between individuals, intimate distance is the space between members of a couple or family, and social distance the link of an individual to other members of a community or social structure within a given territory.

Thus, it could be postulated that the first level of genetic identity corresponds to the genetic constitution of the person whether dead or alive in an objective sense at the most intimate level. If understood in a reductionist or determinist manner, the person will be assimilated to this constitution. Yet, it is at this level that the most fundamental personal choices must be guaranteed if individual control over the generation and the uses of DNA and its genetic information is to be ensured.

The second level, that of genetic individuality, translates the phenotypic expression of a person in a given family, culture and moment in time with his/her individual susceptibilities, predispositions and risk factors. Individual genetic information is necessarily familial and trans-generational. More precise diagnoses often requires family participation. Thus traditional confidentiality and access rules as well as intra-familial responsibilities or immunities will require a reformulating and differentiating of privacy concepts within the familial context.

The third level, that of genetic integrity, recognizes the social sphere of human genetics. The social realisation of genetic integrity depends on its social image and on prevailing values. It is at this level that operational mechanisms for socio-economic protections as well as the conception of state policy should function so as to limit stigmatization and discrimination.

The realisation of both the identity, individuality and integrity components and their personal, familial and social contexts into what might be termed the «genetic unicity» (genecity) of the person depend on this protection and promotion but also on the formulation of ethical principles specific to the context of human genetics.

Foundations for «infogenic» ethics

Privacy has traditionally been seen as a personal freedom and protection from State interference. From a property right, to a

personal claim against the State, it has evolved to include protection from interference in relationships between individuals as well as safeguarding personal information, lifestyles, contraceptive and reproductive choices, and the family as a distinct social unit. This evolution is particularly important for human genetics where the polymorphic nature of genetic information (individual, familial and universal) and its concomittant choices extend well beyond the sole individual.

Indeed, while genetic uniqueness may be scientifically provable as a foundation for genetic privacy it does not suffice. This is because as mentioned there are many levels of relationships involved and important political and social choices surrounding human genetics. Here, public interest is inseparable from private relations. Interestingly, while public and private interests have always been seen in opposition, the promotion of genetic privacy as a liberty interest of the individual in the context of the three levels of relationships described herein renders them complementary. It also requires the conception of ethical principles that reflect the polymorphie and probabilistic nature of genetic information and protect and permit its circulation.

What is needed is the further development of the ethics of risk, of care and of responsibility. Already, these principles are emerging in general bioethics theory. Based on these approaches and applying them at all three levels of relationships just described, the basis of «infogenic» ethics could be what we have called the principles of reciprocity, mutuality and solidarity.

Reciprocity applies at the levei of the physician-researcher-patient relationship. In return for patient participation and contribution to the advancement of science, the physician-researcher must not only provide information but also alternatives and real choices as to the reception of results (or not), DNA banking, sharing, coding, and access by other researchers (and this beyond the lifetime of the person).

Likewise, mutuality implies exchange but this time within the confines of the family where the usual rules of absolute individual control are affected by the familial nature of genetic information. Drawing on the well-known principle of non-maleficence and the newer ethic of care, the moral duty to communicate relevant, at-risk information to family members so as to prevent foreseeable harm is a direct application of familial mutuality through responsibility arising from the relationship itself. This is distinct from legal liability.

Finally, solidarity applies at the level of the State which in return for patient and family participation in screening and testing should

provide the necessary infrastructure for free, universal and equitable access to services and for the voluntary exercise of such choices without discriminatory social or economic consequences.

In conclusion, in order to respect genetic integrity, rather than legislating sector by sector as was the case for economic, personal, medical and social information, an integrated approach is essential. Genetic information has *all* these characteristics. This goal of an integrated approach may well be the catalyst for new models of privacy. Informational self-determination is both individual and collective. The recognition of the personal, familial, social and even universal nature of DNA itself (at the level of the species) and of the need to protect our genetic heritage as the common patrimony of mankind can form the outer framework of the possible realisation and free exercise of genetic privacy based on the inner framework of the genetic integrity of the person and on the ethical principles of reciprocity, mutuality and solidarity.

INFORMGENICS AND PRIVACY

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Introduction

A new kind of information is emerging in our world, information about ourselves, about our essence, that regardless of our literacy level will capture our interest and, what is worse, the interest of others: genetic information.

Although the so-called Human Genome Project has only just begun, there are few doubts that during the next two decades a vast amount of genetic information will start to emerge and will have a major impact on our lives as individuals as well as members of our society. Genetic tests based on recombinant DNA technology are already being offered to health care professionals and, through them, to the public. Today, they are limited to a handful of genetic disorders, but in the future they will reveal not only our predisposition to suffer multifactorial diseases such as cancer, but even to behave in a predictable way under particular circumstances. Despite the importance of this new category of human knowledge, that we can call informgenics (the science concerned with the gathering, manipulation, classification, storage, and retrieval of recorded gene knowledge), there is no specific legal regulation in most countries to protect the individual from an unwan-

ted use of his/her genetic information. This argues for a careful, anticipatory regulation of the application of this new technology and the use of the information derived from this application. Nevertheless, we should realize that we have severe limitations in our ability to anticipate the consequences of a new technology. Accordingly, our approach should be to establish a new regulation to protect the individuals' rights based on our current knowledge, and subsequently, to develop a mechanism of careful monitoring for signs of danger, and rapid response when they appear.

Bases for legal regulation of genetic information

1. Ownership of genetic information

As a general principle, genetic testing should not be required for any purpose other than for criminal justice or paternity identification. In those cases, analysis of DNA with the sole purpose of individual identification does not damage the individual's rights any more than any other form of criminal or paternity investigation. Thus, with this exception, the right to genetic privacy must prevail over any other right. Institutions, public or private, or individuals should not have the right to analyze the genetic information of another individual without consent, even if this analysis is beneficial for society, for the individuals themselves, or for their offspring. As a rule, any information derived from genetic analysis should be treated as any other information derived from medical practice. The individual should be entitled to all rights regarding this information, and the physician should guard this data according to the rules of professional confidentiality. In the disclosure of test results for particular diseases such as Huntington's Chorea, good medical practice and common sense would dictate that the patient should be counseled and assessed in order to ascertain the likely effects of the information. However, the patient should always be entitled to be informed even in situations where the geneticist may foresee how such information could cause harm to the patient, and even influence him/her to commit suicide.

2. Determining the genetic information

Genetic tests should be performed by physicians who have been adequately trained in molecular genetics. With the anticipated expansion of genetic testing, the demand for clinical geneticists and counselors will increase in the next few years. However, the current increase in this pool of professionals will not satisfy the increase in demand. As a result, more non-geneticist physicians and health professionals will use genetic tests, and quality control

in performing these tests will decrease. Unfortunately, unless health care professionals adequately understand how to use this technology, considerable harm may result from genetic testing. Thus, quality control and adequate training are both necessary to make this technology effective and safe. Quality control can be achieved through proficiency testing programs for laboratories that perform and interpret genetic tests.

3. Employment-related testing

If pre-employment testing becomes widespread, people with positive genetic test results may be unemployable, even in the case of late onset diseases. If this group of people require government support, it could generate a significant new economic burden. In contrast, the absence of genetic testing for employment purposes would allow these people to work for a number of years, in many cases, without significant differences from the standard population. Accordingly, genetic testing as a requirement for employment should be forbidden. However, since genetic analysis can identify possible hazards in the workplace and will allow the improvement of safety measures, these analyses, when appropriate, should be an option for the employee. Genetic analysis should be made by a third party, completely independent of the employer, and with the sole purpose of employee protection. Nevertheless, any disclosure of genetic analysis for this or any other purpose, should require the consent of the individual. Employers who do not perform genetic testing for a susceptibility, when this becomes common practice, should not be liable for failure to detect an employee's propensity to suffer a work-related condition. However, if a hazard is identified by means of voluntary genetic testing among employees, the employer should make the appropriate changes to reduce or eliminate the hazard in the workplace. By performing the voluntary genetic testing through a third party, and by not allowing the employers to keep employee records on genetic and other medical information, we will prevent sharing of medical information among companies. Additionally, these third parties should be open to unlimited liability in the event that the professional confidentiality is violated. All employees should have unrestricted access to their genetic and medical records.

4. Insurance-related testing

One of the most serious problems regarding genetic testing will be the further increasing demand for more extensive genetic information before an individual is eligible to receive some public or private benefit. The most obvious cases are health and life insurance; however, other less obvious situations will certainly appear later. It will be tempting, for instance, to know the health

condition of an individual before granting a long-term credit, or to know the intellectual potential of a student before granting a scholarship. It would be unacceptable to use genetic testing in most circumstances, regardless of the goal (i.e., to keep a company's medical insurance costs as low as possible by having a work force free of potential disease, or to reduce pension costs by hiring people with a high probability of death around 60 to 65.) Accordingly, no genetic testing should be required to obtain any benefit or service, public or private.

Health and life insurance deserve special mention. One risk of banning genetic testing for the purpose of obtaining health or life insurance is that people who are aware of their increased risk for disease may seek to purchase more insurance than they ordinarily would. If the insurance company is not allowed to test for an increased risk, it will sell insurance to these people at a regular premium. Eventually, the insurance company will lose money or be forced to increase the premium. Consequently, increased premiums will allow fewer people to buy insurance. Nevertheless, if genetic testing is not excluded, many more people will join the millions of those in many countries, who are already without any form of health insurance. In the most developed nations, the state may be required to provide coverage to people who cannot afford private insurance. In other words, additional funds will need to be raised through higher taxes, resulting in the burden being place on employers and employees who will be the end-payers. At least, by excluding genetic testing, we preserve both genetic testing and the element of risk to the insurance industry.

5. Prenatal, preconception, and preimplantation testing

Eugenics is practiced every day throughout the world through prenatal, preconception or less commonly, preimplantation genetic analysis. If a fetus has a serious disorder, the parents may decide to abort it. Even if they have legal right to do so, maternal and fetal autonomies are in conflict when termination is considered in any case, including the diagnosis of a molecular defect which leads to a genetic disease. Two elements involved in this issue deserve special consideration. One is public: In a world in which the health care cost is constantly increasing, a government might be tempted to reduce this economic burden through careful eugenics. If there is a difference between the early eugenicists and those who would impose genetic testing on the population today, it is not in motivation, but in the accuracy of their methods. The same economic reasons were used in Nazi Germany from 1934 to the end of the World War II. Governments should not use the potential of this technology to solve economic problems. Accordingly, no genetic testing should be mandatory in any

case. This decision should remain the choice of the individual. However, the government should counsel the public properly and extensively regarding the benefits of adequate genetic testing, and should encourage and facilitate this analysis when the disease is treatable. The other element involved in prenatal or preimplantation analysis is personal. For instance, today it is possible to use genetic testing to identify the sex of the fetus. Furthermore, it is possible to identify the sex of multiple embryos before implantation. Unless the test is made to exclude any serious disease linked to the X chromosome and in the absence of any other test, genetic testing for sex identification should not be permitted as it represents a form of discrimination.

6. Predictive testing

Genetic information should remain strictly confidential between the physician and the patient. It is the individual who owns genetic information. Accordingly, any decision regarding disclosure of this information to a third party, including genetic relatives, should remain strictly the individual's choice. This is already an area of conflict in clinical genetics. Prior to counseling a family, confidential information is gathered regarding medical conditions and relationships, among others. Such information may not be divulged without permission of its owner (or guardian), even though knowledge of a diagnosis such as Huntington's disease may be important to those at risk. In a hypothetical case, a family consisting of a widowed father, his two children and their spouses requests counseling and predictive testing for an adult genetic disorder of which the children's mother died 2 years ago. Her father and two sisters were also affected by the disease. Linkage analysis is available, and blood samples are requested from all appropriate individuals, including the two affected sisters who are living in long-term care facilities. The husband of one affected sister refuses to allow a blood sample to be taken from his wife, and the lab has determined that linkage analysis for the condition will not be informative without her blood. There are no quick solutions to this dilemma and no one correct course. It may be argued that an essential blood sample for molecular analysis belongs to the family, but patient autonomy should always be considered first. Reassuring the family that results are given individually and that there will be no discussion of other results may alleviate the concerns regarding loss of control over personal information. The following concerns regarding confidentiality of results for predictive testing must be considered: Not conveying results to other family members without permission; not conveying results to outside agencies; autonomy of the individual to either refuse to give blood to enable family studies or to release results; obtaining truly informed consent for studies, and the use of minors for predictive testing.

7. Genetic information databases

Identity databases

The use of genetic testing to diagnose or predict the disease should remain a medical tool to improve the health of the population on an individual basis. In no case should it become mandatory, and neither government nor any other institution nor any individual should use this information for any other purpose than to improve the health of the individual. Genetic databases based on compulsory sampling should be limited to identity information, as today restriction fragment length polymorphism (RFLP) analysis is understood, that is based on anonymous genetic information, on individuals convicted of violent crimes. No extra information regarding genetic traits linked with diseases or behavior should be used for the construction of these databases.

Genetic registers

The need to maintain records of affected families became especially important with the advent of prenatal diagnosis, which offered the possibility of preventing further cases in a family. The introduction of recombinant DNA technology has emphasized the importance of genetic registers because they provide the means for storing DNA data on affected families. Several general genetic registers have been established in various Centers throughout the world –MEGADATS (Indiana, USA); RAPID (Edinburgh, UK); National Register (Leuven, Belgium); GENFILES (San Francisco, USA); GENTIC (Marseilles, France); PRUFILE (London, UK). Some of these, maintained for ease of storage and retrieval of clinical, genetic, and laboratory data, include information on individuals who have banked DNA for use in future genetic tests. These registers will become increasingly important in the future as they will be the means for monitoring services or therapy, diagnostic reference, epidemiology, research and prevention.

The purposes of these computerized registers should be tracing, following-up and counselling individuals at high risk of transmitting a serious genetic disorder to their offspring. This system should be entirely voluntary. The full agreement of each individual's family doctor should be first obtained, and individuals should only be included with their full knowledge, approval, and expressed permission. Relatives who may also be at risk should only be contacted with the permission of both the original family member as well as the relative's family doctor. The computing system should have very strict safeguards for confidentiality, and access to its information should be limited to only the doctor dealing directly with members of the family. Individuals should be entitled, by request, to be told what data is being held on them, to have access to the data and, when appropriate, to have such data corrected or deleted.

8. Conclusion

The right of the individual should always be paramount when considering the use of genetic testing. Exceptions should only be genetic testing in cases of criminal or civil proceedings which require positive identification. Genetic tests should be performed by properly trained physicians, using appropriate quality control measures. Strict confidentiality of genetic information should be meticulously enforced. Genetic testing as a requirement for employment should be forbidden, but may be used voluntarily to identify potential hazards in the workplace. Genetic testing should not be required to obtain any benefit or service, public or private. Genetic testing should not be mandatory in any case. Genetic testing for prenatal, preconception, or preimplantation sex identification should not be permitted unless the test is made to exclude any serious disease linked to the X chromosome and in the absence of any other test. The right of the individual to either refuse to give blood to enable family studies or to release results should prevail. Genetic databases should be limited to identity information on individuals convicted of violent crimes and should not contain other genetic information. If genetic registers are established, data storage should be voluntary and strict confidentiality of the stored data should be maintained and guaranteed. System users should ensure that no personal genetic data are accessed, destroyed or disclosed without expressed consent.

GENETIC LEGACY AND CULPABILITY

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A human being's genetic information is stored in the nuclei of his or her cells in a double helix of deoxyribonucleic acid (DNA). The DNA of each haploid cell is made up of some 3 million pairs of nitrogenous bases, occupying a total length of approximately 2 metres. However, not all of the DNA length appears to have a specific function. More than 50% of the genetic material is composed of repeated sequences the function of which, as of today, is not known. Furthermore, only a small portion of the bases which form genes directly code production of a protein. As a result of all this, and assuming the average length of a gene to vary from between 1,000 to 2,000 base pairs, the estimated number of structural genes present in the genetic material of a human being appears likely to be somewhere between 50,000 and 200,000.

All this genetic information is finely bundled into 23 homologous chromosome pairs, half of which are of from the father and half from the mother (one chromosome of each pair). Chromosomes are the vehicle of inheritance. Their behaviour in cell division constitutes the basis of Mendelian laws of inheritance.

The harmonic functioning of the set of genes transmitted generation to generation, in combination with the effect of the environmental factors to which man is exposed throughout his life,

determine the human being's physical and psychic development. It is estimated that each person carries a certain amount of genic «defects», ranging from four to 10 in number, though most do not cause the individual any problem. On the other hand, today a total of more than 6,000 different disorders are known to be caused by genetic defects.

It is estimated that some 2-5% of newborns present some type of hereditary disease or congenital defect. These problems account for 30% of paediatric admissions and are one of the leading causes of infant mortality and morbidity. Many are the illnesses which, though not fitting a simple Mendelian inheritance pattern (approximately 10% of adult pathological conditions), currently appear to have a large genetic component. Clear examples of this latter group include certain psychiatric disorders such as schizophrenia and manic depression, diabetes, epilepsy, certain pathological cardiovascular conditions and tumours.

As can be gathered from the foregoing, diseases originating in human genome alterations are an immensely important public health problem. What is more, genic defects have unique characteristics; they represent a pathological condition that produces great stress and anxiety for individuals and families and often generates feelings of guilt in the persons presumed to have transmitted the defect. This feeling of guilt gives rise to many domestic, marital, generational and family problems and to conflicts between families and society at large.

There are diverse reasons which account for said feeling of guilt, and we can classify them as follows:

1. *Individual health reasons.* In general, genetic alterations bring on serious health problems for which there is no effective treatment and, in most cases, for which there is not even a palliative treatment. The parents of a child with Down's syndrome feel responsible for the altered chromosomes that saddle the child with moderate mental retardation and limit his chances at a normal development. The father and/or mother of a child with a simple Mendelian inheritance problem (dominant, recessive or sex-linked) feel responsible for the grave and irreparable problems transmitted to their children, even though they objectively understand that they could do nothing to prevent the disorder. They feel responsible for their child's different than «normal» genome and consequent deficiency.

2. *Family reasons.* Genetic defects cannot be considered solely as individual problems, but must be seen as a family problem. The diagnosis of a genetic alteration in a person has a direct

or indirect impact on all members of the family, as each one is thereafter a potential carrier of the same disease. The sensation of guilt or responsibility for involving other family members forms part of the complex psychological process triggered by these stressful situations.

The major genetic breakthroughs made in recent years have allowed us to establish the location of numerous genes, thus enhancing the diagnostic possibilities for an increasing number of human diseases. Today we can ascertain not just the cause of a given defect in a person, but also the likelihood of an individual being an asymptomatic carrier of a genetic disorder. In other words, a person can know may years ahead of time the probability of developing a certain genetic disease in the future, though the age of its onset continues to be an unknown.

Huntington's chorea is a very clear example in this respect. This pathological condition is an autosomal dominant neurodegenerative inheritance disorder (50% risk of transmission) characterized by the presence of involuntary movements (chorea), and on occasion accompanied by psychiatric symptoms and intellectual deterioration. Symptom onset age is variable (between childhood and sixties), though it generally commences from 35 to 45 years of age. This means that the disease's first signs very often make their appearance after the person has formed a family. The disease leads to death in approximately 15 years.

Experience has shown us that the decision on whether or not to undergo Huntington's chorea pre-symptomatic screening frequently poses major personal and family dilemmas. This situation often generates a feeling of guilt secondary to the conflict of personal and family interests.

The decision not to undergo the study entails greater family-planning difficulties, and at the same time excludes the possibility of knowing the specific risk (50% or none) to offspring. However, a positive result, reveals not only the heightened risk to descendants, but also saddles the husband/wife, children and relatives in general with the burden of knowing that in some years (few or many) he or she will cease to be the person they all know and love. Does a person not have the right to continue living, and let others live, without knowing? Whose rights should prevail? On the other hand, it must be kept in mind that diagnosis of a person involves direct diagnosis of his progenitor at risk. In cases where the progenitor does not yet display symptoms and wishes not to know his state, whose autonomy should be

respected, the child's or the parent's. How can either one avoid feelings of guilt?

A similar conflict arises in connection with the decision on carrying out prenatal tests, as these sometimes represent a clash between the rights of the at risk mother/father and their desire to bring a healthy child into this world. If an at risk mother does not wish to know whether or not she is a carrier, she can undergo what we call an exclusion test. This test determines which of the two maternal chromosome has been inherited by the fetus: the one from the healthy grandparent or one from the diseased grandparent. If the fetus inherits the healthy grandparent's chromosome, the future child will be healthy. Otherwise, the fetal risk of suffering the disorder will be 50%, like the mother. This means that the couple will have to make a decision with respect to continuing the pregnancy or not, taking into account that the fetus will have a 50% chance of being born healthy, and that even if affected, the child could live half a lifetime without any problems.

Lastly, we must keep in mind that even a negative result (no disease) can also produce guilty feelings. It is not unusual for disease-free persons to feel responsible for having been chosen or fortunate in comparison to their siblings. This situation mainly arises when simultaneous testing of two or more family members is favourable in one case and unfavourable in the other(s).

3. *Social reasons*. Society's attitude toward a genetic problem is a most important factor in how individuals perceive themselves as responsible for or «guilty» of the problem affecting them and their families. Society has maintained and still maintains an attitude of absolute discrimination and rejection toward hereditary disorders. We must not forget that not long ago, some states and nations even passed laws which directly violated the rights of the individual in an attempt to rid society of specific diseases.

Today it is hard to imagine the kind of brazen social discrimination suffered in the past by persons having some type of genetically caused physical defect. Yet the application of new molecular technologies is giving rise to another type of genetic discrimination much more sweeping than that of the past. Today there is a tendency to discriminate against an individual or family members solely on the basis of the differences (real or supposed) in their genetic legacy from what is considered the «normal» genome. The people apt to suffer this type of genetic discrimination are: i) asymptomatic carriers of genes that increase the likelihood of

incurring a given disease; ii) asymptomatic heterozygote (carriers) of recessive or sex-linked recessive genes; iii) relatives of persons with a real or supposed genetic disease.

At present, many cases of genetic discrimination have been denounced, primarily in connection with job opportunities and health-care coverage in private companies. At the same time, the Human Genome Project continues to broaden our understanding of the genetic basis of many other diseases, with the consequent development of new diagnostic tests for many disorders. The role of health-care professionals, especially clinical geneticists, is key to the numerous ethical conflicts and situations brought about by this new technology. It is important to make the public aware of the possibilities for diagnosing and preventing genetic disease, and of the attendant personal, family and social problems. But it is also fundamentally important to provide the necessary psychological support and aid to those in such need. Lastly, as a complement to such an endeavour, it is absolutely indispensable that we establish a legal framework that protects the public interest and avoids the possible abuses which could be generated by misuse of confidential information.

BIOLOGICAL PATERNITY TESTING AND SECTION 632 OF THE SPANISH CIVIL PROCEDURE ACT

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Introduction

Overview of the issue

Advances in medical-biological techniques combined with the reform of the Civil Code's filiation provisions, in particular section 127, which allows «paternity and maternity investigation by means of *all kinds of tests, including biological ones*» in paternity suits, have pierced the mystery veiling paternity over the centuries. Today paternity and maternity can be deciphered with the help of the aforementioned biological tests. The incorporation of these technical advances into the Civil Code represents a genuine novelty in our legal system and has been widely praised within the world of civil law. The admission of these techniques, however, has not been accompanied by legal regulation of measures for their actual use and of other question regarding their relative weight and probative value. These issues have been addressed by the Spanish Supreme Court and an extensive body of legal doctrine and case-law has been generated, and in some aspects consolidated.

Within the broad range of questions not directly regulated by the reform of the Civil Code, *one of the thorniest issues* on which the

Supreme Court has made no direct judgement is the question of the current validity of section 632 of the Spanish Civil Procedure Act (CPA) in the face of the highly reliable results attained through biological testing, in particular haematological or blood group tests, serostatic tests and, above all, DNA typing.

Section 632 of the CPA sets down that: «Judges and courts shall evaluate expert evidence according to the rules of sound critique, without being obliged to uphold the findings of the experts». The central theme of my brief analysis is as follows: *given the high degree of reliability attained by the above-mentioned tests, will judges and tribunals still be able to make use of the discretionary power granted them by the Civil Procedure Act when assessing the weight of expert evidence, or, on the contrary, will the expert findings necessarily form the basis of the judgements they render in filiation disputes.* The question, in short, is whether we should conclude that judges and courts must be required to adhere to biological evidence which in most cases is more than 99% accurate, irrespective of whether the other evidence heard supports or rebuts the results of the biological evidence, or, conversely, that the judge should be able to freely evaluate the expert findings.

Many other salient questions arise in relation to this central issue. Can judges and courts refuse to allow such tests to be conducted and submitted as evidence? Should it be the possible, as is already the case in some of the countries in our setting, to enforce mandatory testing of individuals who refuse to submit such evidence? I will not take up these questions, however, and instead confine myself to the question posed above as to the applicability of CPA section 632 to this area in light of the advances being made in biological paternity tests.

Biological tests and their probative value: the haematological or blood group test, serostatic tests and DNA typing

Before taking up the analysis of the central issue raised above, I think it would be helpful to give a brief up-to-date description of the most important and most frequently used biological tests, in order to enhance our understanding of their content and their degree of reliability.

1. Haematological or blood group test

This test is based on the biological principle that all traits which are genetically inherited come from either the father or mother, such that what is not inherited from one must necessarily have

been inherited from the other. In the blood group test, once the mother's, child's, and presumed father's genetic material is known, the genetic material common to the child and mother (undoubted) is discarded, and the child's remaining genetic material (which must necessarily have been inherited from his or her biological father) is checked against that of the presumed father. Paternity is thus excluded or confirmed as a possibility.

In order to determine filiation experts study the most important and stable, hereditarily transmitted blood traits which are independent of age, disease and environment and easy to objectively determine. Among the different «polymorphic markers» normally used, the HLA test applied to chromosome 6 of each individual stands out for its documented probative value. Due to the difficulties involved in obtaining the sera and materials required for conducting this test, it is usually done in cases where other systems have not wholly confirmed or ruled out paternity.

When this test is carried out the first goal is to verify whether the paternity of the person in question can be excluded or, on the contrary, be admitted as possible. If paternity is not ruled out, the next step is to determine the likelihood that the person is the actual father. This involves going on to the serostatic test.

2. *Serostatic test*

Where paternity has not been excluded, its probability is calculated. The Essen-Möller formula is used.

$$(X, Y): W = \frac{X}{X + Y} \times 100$$

Where:

X = the frequency with which a specified genetic marker possessed by the child is found in the actual father.
Y = the frequency with which that same genetic marker is generally found in the population of other men (not the father).

Associated with the numbers obtained from the paternity probability obtained via the above formula are the so-called «verbal predicates». These consist in translating the numerical values denoting paternity plausibility into words. According to Hummel's table, paternity is considered as practically proven when the formula yields a 99.8% probability. Results of between 99% and 99.7% are taken to indicate a high likelihood of paternity, which is considered very likely for results of between 95% and 98.9%, and as simply likely when the percentage is between 90% and 94%. For anything below 90%, paternity is considered as uncertain.

The Essen-Möller formula has been adjusted for proper application to special, particularly difficult cases, such as where the possible paternity of several men must be considered. Where the mother has had several sexual partners, the serostatic test, in conjunction with additional formulas and computer programmes devised by Hummel and his collaborators, can be used to provide direct or positive evidence of the paternity of one of the possible fathers and, at the same time, indirect evidence of the non-paternity of the others.

3. DNA typing

This is the latest innovation in biological paternity tests. It consists in an attempt to decipher the chemical alphabet written into a person's DNA.

This test offers a series of advantages with respect to the ones analyzed above, given the higher degree of reliability attained in doubtful or special cases such as incest or where the possible paternity of two brothers is to be determined. It can only fail in cases where the presumed fathers are identical twins.

Analysis of section 632 of the CPA and the principle of discretionary evaluation by the judge

Sections 1243 of the Spanish Civil Code states that provisions of the Civil Procedure Act shall be applied in determining the value of expert evidence and the form in which it should be taken. As already pointed out, with respect to expert evidence section 632 of the CPA proclaims that «judges and courts shall evaluate expert evidence according to the rules of sound critique, *without being obliged to uphold the findings of the experts*».

Procedural doctrine has construed the letter of CPA section 632 to mean that expert evidence shall be freely weighed by the judge. This conclusion begs the question of how a judge could fail to uphold an expert opinion which provides knowledge that the judge most likely does not have. This question draws the reply that no matter how the system of discretionary decision may be interpreted, *the judge should always give the critical reasoning behind the admission or rejection of a given piece of evidence.* «As a result of the application of these systems of evidence, in which the parties are left defenceless, the legal, doctrinal and juridical expression has been coined that a given piece of evidence does not bind the judge. Certainly, this is not true, for if it did not bind the judge, the trial activity undertaken by the parties in support of certain facts and statements would serve no purpose. *What*

this expression means is simply that no specific evidence obliges the deciding body as to its findings. In this sense, applying the rules of sound critique, the reasons for which the validity of a fact verified during the proceedings is not embraced should be given. But certainly the trier of fact is bound by the proof» [1].

Naturally it must be recognized from the very outset that the issue before us here could not have possibly been contemplated at the time when the CPA was drafted. Today's technical advances did not yet exist and, consequently, an expert opinion was precisely that: a report by an expert in a given field which could even be rebutted by opposing reports from other experts. This remains true in many cases but has changed with respect to situations such as the ones analyzed herein. Still, the issue before us is much more pressing than simply that of the evaluation of expert evidence by judges. The question here is to what extent can a judge's decision depart from biological evidence which affords, if not 100% accuracy, close to it. Furthermore, as has been stated by the Supreme Court on numerous occasions, current regulation of filiation disputes has evolved from the principle of formal truth to that of material truth.

Should these tests not be considered, more than expert evidence, genuine factual circumstances of the proceedings, genuine proven facts?

In the very extensive Supreme Court case-law in connection with disputes involving persons who refused to submit to genetic tests, the high court has given a preponderant value to such refusal and proclaimed that «the refusal to submit to biological tests, though not entailing a *ficta confessio* [tacit admission], does represent a valuable indication which taken together with other probative elements permits deduction of paternity» [2].

The Supreme Court has also stated (implicitly on some occasions, explicitly on others) that the two considerations which must be present in order for the judge to declare paternity are: first, the possibility of the woman's impregnation, and, second, the obstructionist refusal of the defendant to submit to the performance the above-mentioned tests.

It would appear reasonable to conclude that if the Supreme Court can on the basis of presumptive evidence and, above all, pursuant to the final subparagraph of section 135 of the Civil

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[1] Vázquez Iruzubieta, Carlos: «Doctrina y Jurisprudencia de la Ley de Enjuiciamiento Civil» [Civil Procedure Act Doctrine and Case Law], *Revista de Derecho Privado*, Madrid, 1984.

[2] *Inter alia* the Judgements of October 14th 1985, June 27th 1987, November 26th 1990, May 14th 1991 and February 2nd 1992.

Code, conclusively deduce paternity from the presumed father's refusal to submit to biological testing and the above-cited possibility of the mother's impregnation, then, all the more reason why the Court should hold the biological tests to conclusively determine paternity or non-paternity in cases where such tests have been performed. The reasoning behind my conclusion is that if in the first case the Court hands down a judgement of paternity on the basis of a mere presumption, the second case provides all the more grounds for a similar ruling. Therefore, where the tests are carried out, given the highly reliable results they furnish, I think it improper for the Court to use the discretionary powers conferred by CPA section 632 to hold differently than the results of the expert biological opinion.

This opinion obviously refers exclusively to the question set out above, that is, the applicability and validity of CPA section 632 in cases where biological testing has been performed. I do not analyze the question of the judge's discretion as to whether or not to admit such tests as evidence, or his or her a posteriori discretion to decide custody of the child, or other issues of such nature.

The initial conclusion reached above prompts new questions:

1. In such proceedings would expert biological evidence therefore suffice as sole evidence to sustain or refute paternity?

2. What would occur in cases where the results of the biological evidence are opposed by evidence to the contrary?

3. Cases involving more than one possible father, identical twin brothers (the only circumstance in which not even DNA analysis is reliable), and problems arising in connection with the minor's right to child support, succession rights, etc.

Conclusions

1. The Spanish Supreme Court's doctrine as regards section 632 of the Civil Procedure Act proclaims that while judges and courts are free to weigh the expert evidence taken during the proceedings according to the principle of sound critique, the conclusion reached in their evaluation thereof *shall never be contrary to «a patently obvious fact or to the most elemental logic»* [3]. Thus, though the weighing of such evidence is discretionary with the judge, «the latter may not proceed

[3] Supreme Court Judgement of December 4th 1989.

arbitrarily, but pursuant to the rules of sound critique, which are those of logic and common sense» [4].

The Supreme Court has thus far not entered any judgements denying the evidence-evaluation discretion conferred on judges and courts in paternity suits by CPA section 632. Nevertheless, from the legal doctrine described above we might infer that given the high degree of reliability offered by biological tests, and in particular by DNA analysis, a judge entering a judgement different than that suggested by the results of the biological tests would have to base such decision on a wealth of very reliable evidence of other kinds (testimony, confessions by the interested parties, documents). Although our case-law as yet records no instances of such a situation arising, it is no less true that Spanish judges, while ever more recognizing the high probative value of these tests (not only where they refute, but also whey they establish paternity), continue observing the letter of CPA section 632 and Civil Code section 135 in order to support the exercise of their interpretative discretion [5].

2. From the extensive case-law regarding refusal by the presumed father to submit to biological testing [6], it may be concluded that:

   – The defendant's refusal to submit to the said tests provides an indication of inestimable value.

   – The «lack of direct evidence of the facts brings into play the presumptions contained in the general provisions of sections 1249 to 1253 of the Civil Code, without prejudice to the specific provisions set down for particular situations, such as occurs with section 135 of the same Code, which, due to its specificity prevails over the general rules and allows inference of filiation by means of the use of analogy». In this regard the Judgement of April 5th 1990 is extremely interesting. In a similar case, after reiterating the above-described doctrine with respect to the possibility of proclaiming paternity by analogy, the Court stressed that *«the principle that the trier shall be free to examine evidence and to reasonably weigh and evaluate the same tends, in short, to pursue the trial principle of material truth*, [...], for which the last subparagraph of Civil Code section 135 turns out to decisive, insofar as concerns adequate legal grounds. The

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[4] Supreme Court Judgement of May 18th and February 13th 1990, *inter alia*.
[5] Supreme Court Judgement of February 7th 1986, *inter alia*.
[6] Supreme Court Judgements of March 18th 1988, January 24th 1989, and January 19th and April 5th 1990, *inter alia*.

said subparagraph alludes to and mentions as a closing reference "other facts from which filiation is inferred by analogy", an indicative phrase –as declared in the Judgement of December 7th 1988– which no doubts refers to indirect evidence that is of special significance in the absence of the basic facts mentioned in the oft-cited CC section 135 (express or tacit recognition, possession of legal filial status, and cohabitation with the mother during the period of conception), *or when no direct proof of generation exists due to the defendant declining to submit to the relevant biological tests*».

3. From the foregoing analysis, and taking into account three already-mentioned trends, namely (i) paternity law as it stands today is suffused with the principle of material truth (ii) biological testing and DNA typing in particular have attained a high degree of reliability in establishing and/or ruling out paternity, and (iii) as demonstrated by the case-law in this respect, our Courts, making use of their discretionary evidence-evaluation powers, are assigning greater weight to the results of biological testing, where such has been performed, than to all other types of evidence (or more significantly still, have interpreted the refusal to submit to such testing, together with the other circumstances, as a fact from which paternity can be deduced). *I think it appropriate to conclude that biological evidence, in view of the high degree of reliability it offers both in confirming as well as in refuting paternity, should now be considered by the Courts as «direct evidence of generation» within the meaning of Civil Code section 135, and that the Courts should be therefore denied the discretionary authority conferred upon them by CPA section 632, whereby they were empowered to weigh such evidence freely and thus enter judgements contrary to the results of biological tests which in most cases offer accuracy of 99% or greater.*

4. Just as case-law has found in the final subparagraph of Civil Code section 132 grounds for a presumption of paternity in cases where the supposed father refuses to submit to paternity tests, I believe the expression «direct evidence of generation» from that same section could be broadly interpreted so as to admit the results of biological tests as direct proof with respect to which judge does not have discretionary powers as to its probative weight. In any event, nobody could argue with the assertion that a paternity or non-paternity judgement based solely on the biological test evidence offers greater certainty than one based on mere presumption of paternity attendant upon the refusal to submit to such testing. Yet, nobody is startled or alarmed by this solution as found in our case-law, and it has in fact received much praise.

In this regard I will once again recall the words of the Supreme Court Judgement of April 5th 1990, which appear to open up a new line of reasoning in the high court's jurisprudence, when it refers to biological tests as «direct evidence of generation» and likens them to such basic facts as express or tacit admission, possession of legal status, etc, taken per verbatim from Civil Code section 135 *ab initio*.

Lastly, I find it necessary to point out, with respect to the view expressed by the Spanish Supreme Court in its well-known judgement of May 21st 1988, «illogical and hard to accept is the unawareness that the techniques now in use in haematological filiation testing offer absolute accuracy insofar as concerns negative evidence», is not true [7], as they are even more reliable precisely when it comes to proving paternity.

With current haematological testing means and techniques it is possible in many cases to rule for or against paternity with 99.73% reliability. Juxtaposed with current DNA typing, where the minimum acceptable probability for an *a priori* exclusion of paternity is 99.9% and the paternity proven criteria which dictate that paternity is only proven when there exists a certainty of 99.73% or higher (which these tests often surpass), and with the fact that 99% accuracy is only considered «highly likely», this prompts a slew of questions as to how can anyone still continue to object to this biological evidence. Thus, given this high degree of accuracy, if we accept that judges can freely weigh the results of this expert evidence and rule other than as thereby indicated, we would be allowing litigation to be decided by such fallible evidence as testimony or documents (certificates of good conduct or of the mother's honesty) or presumptions (cohabitation *more uxorio)*, or possession of legal status. One thing is obvious: once the issue of paternity has been posed, the judge must enter a ruling either for or against paternity, and, under a system that permits and advocates the investigation of paternity if a judge rules counter to the results of the biological evidence because it does not offer guarantees of absolute certainty (and 99% does not seem to him or her to be sufficient), that judge will necessarily have to base his or her judgement on the other classic or ordinary types of evidence mentioned above.

I could conclude by voicing more of the inevitable questions such as: what judge could enjoy more than 90% confidence in his or her decision on a paternity case if the judgement

[7] Ribero Hernández, Francisco: «Comentario a la sentencia de 17 de julio de 1987» [Comments on the July 17th 1987 judgement], *Cuadernos Civitas*.

had to be made on the basis of no other evidence except witness testimony, such documents as are presented in those lawsuits, presumptions and court declarations?

Perhaps nobody has more reason than judges to celebrate the existence of this kind of reliable and effective evidence and of legal rules which permit its unrestricted use.

GENETIC TESTING AND MATRIMONY

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Knowledge of the human genome also raises questions involving matrimony. In some countries, the responses to the existence of genetically transmitted diseases were regulations as to the content and effects of pre-wedding medical certificates. Such laws could be widened to likewise include genetic tests, both for purposes of marital disqualification and to furnish information with a bearing on procreation decisions. Making such tests mandatory, broad disclosure of their results, and the contents and effects thereof may harm fundamental rights such as privacy, equality and freedom.

Matrimony is intimately linked to sexual life and its natural outcome, procreation. This dual reality and all decisions affecting them have always been a cause of concern and moral, religious, medical, psychological, sociological and legal discussion.

In the area of health care, carnal union is linked to the transmission of diseases, primarily, though not limited to, venereal disease. This fear has now been heightened by AIDS, a contemporary scourge with terrifying social impact. As for procreation, the medical world's main preoccupation has been the fight against infertility. The struggle to overcome obstacles to childbearing has even turned to sophisticated genetic techniques.

But birth control is also motivated by demographic reasons, or by individual health, social or economic factors. All these reasons are present in the endeavour to master the laws of inheritance so that offspring may be freed of serious mental or physical handicaps and defects.

In the face of these developments, lawmakers have at times succumbed to the temptation to intervene efficaciously in this process and forestall the harmful consequences of carnal relations. Such legislative action has been a constant, though its influence has varied greatly over time.

Beginning in 1900 Mendel's laws were rediscovered through their application to man. Garrod, with his 1902 work on congenital metabolism errors, and Hurst, with his 1907 research into eye colour, were among the first human genetic investigators, initially focusing their studies on physical features and disease. Their aim was to improve the quality of the human race by manipulating its biological inheritance.

Prior to the triumph of national socialism in Germany, scientific doctrine had discovered that a large number of diseases, physical as well as mental, were of a genetic origin. The scientific movement championing biological evolution grew strong in that country during the 1930s, was embraced by the Nazi party as its own prior to their ascent to power, and promoted by Hitler's government thereafter. As a result, the rise and fall of Nazi doctrines have had a great bearing on all eugenic thinking and on how eugenics is seen by society.

Racial hygiene was based on the improvement of the genetic pool and in its pursuit individual rights were trampled, both in the area of reproduction decisions and in the selection of spouses. Eugenics held that genetic factors determine mental health and moral condition and have a decisive influence on criminality. Under its inspiration, mass sterilizations, legalized euthanasia, and genocide for racial or psychiatric reasons were carried out.

Against such a background, all present-day attempts to influence genetic factors to the benefit of the offspring undoubtedly smack of eugenics and, in principle, triggering an allergic reaction brought on by the memory of Nazi horrors. We must nonetheless point out, however, that scientific actions aimed at eradicating or curing hereditary disease, illnesses or malformations should be seen as beneficial. Their development and application should be encouraged, provided there exist adequate controls to prevent their utilization for ethically undesirable ends and that the essential principles achieved by man through fierce struggles and tragic revolutions be safeguarded.

Eugenics and matrimony

With respect to matrimony, eugenics inspired legislation seeking to make marriage contigent on the potential couple's state of health, so as to avoid transmission of disease within the couple and major risks to the offspring. The United States was the first to dictate laws in this respect. In 1904 New Jersey prohibited persons who had resided in mental institutions from marrying without medical certification of their recovery. In that same year, Ohio broadened the prohibition to alcoholics and victims of contagious diseases. After 1905, beginning with Indiana and Minnesota, prohibition was extended to a large number of other states, although most only required that the man furnish certification of his health status, specifically with respect to venereal disease. The German law of October 16th 1935, with the national socialists firmly in power, required each spouse to present a medical certificate showing they did not suffer from mental illness or a genetically transmissible disease. This law was extended to Sweden and Denmark during the same period, although only as concerned venereal disease.

The aforementioned aversion to any legislation of Nazi origin or inspiration has meant that today many countries have annulled the provisions requiring such certificates (Sweden and Denmark 1968 and 1969) or have not contemplated any similar regulations.

There nevertheless continue to exist countries in which the government requires a medical certificate, of varying content, prior to contracting matrimony. I am not referring here to the possible ground for annulment due to the concealed existence of a venereal disease or other serious contagious illness, which is contained in the legal systems of many countries, but to the lack of knowledge of essential conditions or characteristics of one's marital partner.

This analysis takes up those legislations which require a prewedding medical certificate based on a prior examination, analysis or test, the results of which are included on a document issued by a medical professional as a precautionary measure for avoiding contagion of the other spouse or procreation-related problems. The certificate and the performance of the necessary tests are a necessary prerequisite for the marriage to take place.

In this regard, two main types of laws may be distinguished on the basis of whether they require that tests yield specific results or merely that they be performed.

1. Favourable result required

Some legislations make the marriage contingent on the results of obligatory medical analyses or tests.

The Turkish law of 1921 (articles 122 and 124 of the Civil Code) is paradigmatic. It requires a previous complete medical examination of the future consorts in order to determine the existence of diseases such as tuberculosis, syphilis or epilepsy, which, if detected, may result in the marriage being forbidden or, in some cases, such as tuberculosis, delayed.

Panama, under its law of December 3rd 1928 (section 98.3), provides for the following obligation: «*males* intending to contract matrimony shall previously also file with the Judge a certificate stating that they do not suffer from any serious contagious disease, which certificate shall be issued by a physician». Excepted from this obligation are marriages entered into at the point of death and «those of municipal governments existing previous to the enactment of this Law».

The Chinese marriage law of 1980 (section 6.2) requires a pre-wedding medical examination to determine that neither one of the future spouses has leprosy or any other illness which disqualifies them from marrying.

Most states in the United States maintain the requirement for a medical examination to detect venereal and contagious diseases, epilepsy and narcotic or alcohol abuse. The consequences of failing to furnish such a certificate vary from state to state.

Medical certificates are also a pre-wedding requirement in Mexico (Civil Code sections 97 and 98), Argentina (Civil Code section 187), and Bolivia (Civil Code sections 55 and 56).

2. Examination required; results indifferent

French law (and that of Luxembourg, with the same content) since December 16th 1942 requires the future consorts to undergo medical examination and the issuance of a certificate to be filed with the «officer of the civil state». The nature, content and effects of this certificate, however, differ from those considered above.

Under the Decree of March 17th 1978, the pre-wedding medical examination must, above all, focus on the risk of contagious disease and include the analyses and tests contained in a list drawn up and amended by law. But the certificates (which are valid for 2 months) can only accredit the fact that each of the interested

parties has undergone the tests for purposes of their betrothal. Any other indication as to the result of the examination is excluded (Civil Code section 63). The certificate must only demonstrate that the examination has taken place. The consequences of the examination are specifically excluded from the certificate. The doctor must give the certificate to the interested party along with a health education brochure, a telling indication as to the purpose of the examination.

Hence, the conclusions of the medical examination must not be revealed to the civil officer or to the other spouse and its outcome in no way conditions the possibility of entering into wedlock. As Boulanger has stated, «the entire system rests on the moral conscience of the future spouses», since they are the only ones who know –and each only insofar as concerns him or herself– the result of the examination and can ponder and take decisions as to the possible consequences for their spouse and future offspring.

Today other aspects arising from our present social reality must be added to the traditional concern for the risks of contagion and hereditary transmission. Some are recent diseases such as AIDS. Others derive from new situations such as transsexualism, or surgical sex-change operations justified by contradictions between physical and psychological gender. The possibility of a person having one sex today different from a former one has potentially decisive consequences for matrimony, just as the fact that a person of one sex might harbour conditions which in the future –perhaps after marrying or even procreating– might lead to adoption of the opposite sex.

Legal preoccupation with the physical or mental conditions of potential parents as possible determinants of risks for descendants have not only led to the placing of conditions or outright prohibition on marriage, but also to authorized or forced sterilization of certain afflicted people in order to prevent them from procreating. And here we must distinguish between very different general principles. One possible position is an absolute prohibition of the sterilization or castration of human beings, in whatever form or for whatever reason. Another course is to admit the possibility of such intervention but only with the informed consent of the interested party. And lastly, the third possibility is to allow such actions under judicial control without the victim's acquiescence being necessary.

The sometimes contradictory interpretation of the principles of man's inviolability and the protection of descendants has been subject to different translations.

In the United States there is the classic case of Buck vs Bell. In the majority opinion drafted by Justice Holmes, the Supreme Court upheld the constitutionality of a Virginia law under which Carrie Buck was sterilized in 1927 on the basis of a medical finding of mental deficiency and the risk of said deficiency's possible transmission. The latter concern was supported by the fact that the woman had already given birth to a daughter with signs of similar impairment. The Supreme Court's decision contained clear allusions to reasons drawn from eugenic doctrines. It also alluded to the similarity with obligatory vaccinations.

Sterilization codes exist in Asian countries and these ideas, long rejected by memories of the Nazi experience, are returning today in many other places with renewed strength.

Here in Spain, section 428 of the Criminal Code (drafted in accordance with Organic Act 3 of June 21st 1989) removes criminal liability for sterilizations performed by doctors not only in cases where the patient freely gives his or her express consent, but also in cases of incapacitated persons with «serious psychic deficiency», who, of course need not give their consent. In the latter case, judicial authorization is required and guarantees are provided such as a finding by two specialists, appearance by a representative of the general attorney's office, and pleadings by the incapacitated person's legal counsel.

From the above it may be gathered that an incapacitated citizen may be sterilized, without his or her consent, in order to avoid procreation carrying some risk to the progenitor but, above all, to the offspring and, perhaps, to society.

Genetic testing

The development of genetic screening raises new questions and introduces new factors into the study of the traditional ones. All this leads us to ask whether people wishing to marry can legitimately be required to undergo genetic screening or testing before they enter into wedlock. And if so, what should such testing consist of, to what uses may the results be put, and what might the possible consequences be of a failure to comply with this requirement or of the results themselves?

Social concern with respect to sexual relations and their procreative consequences has hitherto translated into legal provisions for medical examinations geared to very specific diseases (venereal and contagious diseases, mental disorders, tuberculosis, etc.) and to the preparation of a family clinical history. With the advance

of genetic technology –including, obviously, progress in our understanding of the human genome– new questions are being raised (perhaps vestiges of old concerns) which require new thinking and new conclusions.

The possibility –ever greater and foreseeably even more so in the near future– of uncovering facts which involve risks to descendants necessary leads to a review of certain basic concepts. It is once again a matter of tracing the dividing line between spheres safeguarded by seemingly contraposed fundamental principles. The greater benefit –or better stated, the diminishment or suppression of harm to the descendants– may clash with the right to privacy, to freedom or to equality, or with the right to not be discriminated against for reasons of illness or physical defect. The right of all persons to enter into matrimony, to lead their own sex life freely and independently, and to procreate may also be encroached upon. And we must not forget the fundamental rights to benefit from technological and scientific advances and the right to health. Lastly, it must be recalled that human beings have the right to know, but also the right not to know.

The Human Genome Project

Although the popular notion that the project's completion will mean full knowledge has been attained of man and his diseases is obviously incorrect, and though it is clear that knowing the map or its sequences is not enough, undoubtedly when that time arrives, we will have definitively completed the number of known genes and thereby classified an important number of genetic diseases. Gene behaviour will be understood with ever greater accuracy, leading to unpredictable consequences.

We cannot forget, in any case, that each person's genome represents part of that person and to a large degree –though not exclusively– *makes them what they are and what they will be.*

Genomic knowledge may disclose diseases, mutant genes capable of producing hereditary ailments or predisposing us to physical or psychopathological disorders, or individual traits such as inclinations or skills. Genome knowledge's promise for preventive medicine, eternal aspiration of humankind, is unquestionable and of exceptional import. Ever since the discovery that genes are responsible for the hereditary transmission of certain diseases, research has focused on identifying such genes and locating them in the chromosomes; although it should be borne in mind that there are diseases, such as Huntington's chorea, which are caused by one gene, and others by the combination of two or more

defective genes. The renowned molecular biologist Robert Weinberg has pointed out that «during the next decade, we may begin to come across genes that are surprisingly strong determinants of knowledge, affection and other aspects of human function and appearance» [1].

Of course this outlook should not lead us into a biological determinism; we must remember that man's destiny, in addition to residing in his genes, is formed by the environment, medium or circumstances surrounding him and with which he lives, and, moreover, by his free will.

Nowadays we can witness how genetic knowledge is daily divulged in the mass media and is becoming part of the citizenry's cultural baggage. And this aspect is absolutely fundamental, because the children of today –tomorrow's adults– are brought up to be familiar with the concept of genome –their genome– and with the fact that knowledge of the genome, which will soon be possible, can be beneficial to the prevention of diseases and malformations in themselves and their children.

The purpose of a human genome diagnostic test is to determine whether a gene, or genes, is present or absent in a given genome. The use of such tests will increasingly allow us to distinguish between persons with a low, moderate or high risk of suffering a specific disease and, likewise, with a greater or lower likelihood of passing it on to their descendants.

Genetic tests are developed from the methods used for exploring the DNA sequences which form the basis of biological inheritance. Genomic information can allow detection of diseases, the symptoms of which have not yet set in but which are biochemically present. Detection of latent diseases will be more accurate. Tests for detecting diseases before the onset of symptoms already exist; not only diseases, but complex disorders as well.

As Gerar Huber has indicated, the more than 4,000 genetic diseases already catalogued include some of the most serious and deadly, such as cardiovascular disorders, cancer, diabetes, myopathy, haemophilia, Alzheimer's, and other neurological, psychiatric, hepatic and rheumatic diseases, and diverse forms of allergies.

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[1] Quoted by Robert Wright: «Achilles' Helox», *New Republic*, July 1990, pp. 21-31. The quotation here has been translated from the Spanish.

Gene therapy

Doubts as to the right or obligation to know only acquire importance if that knowledge has some utility and is not just mere speculation. Utility is determined by two factors: first, by the possibility of eliminating harm by deciding not to have children, and, second, by actions to remedy or avert pathological consequences.

Although still in its infancy, gene therapy is already a reality. It is possible to exclude or replace a gene and thereby alter a person's unique and singular genome. There have been thoughts and discussions on whether only somatic cells should be altered, wherein only that person's genome is modified, or whether it is legitimate to alter the hereditary line by means of replacing germinal cells.

But there is another way of preventing congenital disorders from arising, once the risk has been detected and prior to conception. And that is the decision not to reproduce. Such determination may be relative, that is, to not have children with a carrier of the same genetic abnormality, in the case of recessive autonomous diseases, or absolute, when the autonomous disease is dominant or linked to the X chromosome. These cases of course are irrespective of whether or not different forms of assisted reproduction are sought.

Prenatal diagnosis

At this point in this reflection I should mention prenatal diagnosis. After conception, and once not the risk but an actual fetal anomaly is established through prenatal diagnosis, the option is abortion.

At present prenatal tests are the usual source of genetic information. Amniocentesis is used to detect genetic biochemical or chromosomic abnormalities. The latter include trisomies such as Down's syndrome; Huntington's chorea and Tay-Sachs diseases are examples of the former. Prenatal testing was initially used to determine the sex of the fetus, which was of special importance in cases of sex-dependent hereditary transmission, such as haemophilia, where the recessive gene is carried by the X chromosome.

In any case, the findings obtained from this prenatal diagnosis precede a decision on *abortion.* In 1968 the medical journal *Lancet* published the first report of an abortion performed in order to avoid the birth of a fetus prenatally diagnosed as having Down's syndrome.

According to Bruno Brambati, «in the future it will be possible for prenatal testing to diagnose life-threatening processes, those of moderate or manifest symptoms or with late onset (such as Huntington's chorea, polyquistic kidney), genetic predispostions to certain diseases (e.g. diabetes, cardiovascular diseases), and even aesthetic traits». «All these things» he continues, «will make genetic diagnosis more acceptable as a test for a greater number of persons who will be able to decide whether or not the newly conceived being should be born».

In any case, prenatal diagnosis leads to a decision on abortion, which is always a troublesome question at the religious, ethical and moral level, as well as legally, and even, psychologically.

Recall, although the issue is a very specific one, that the discoverer of the connection between trimsomy 21 and Down's syndrome, Jerome Lejeune, publicly voiced dismay over his discovery leading to a large number of abortions.

Under Spanish law, section 417 bis 3 of the Criminal Code, in line with similar precepts of other legislations, decriminalized abortion when it is presumed that the fetus will be born with major physical or mental defects. The health of the future child prevails over other fundamental rights.

But if it were possible to know prior to pregnancy that a couple will conceive a fetus with a high –or medium or low– risk of serious disease, malformation or limitation, should it not be obligatory for such knowledge to be attained so that decisions can be taken before, and not after, conception? It is true that in the case of pre-conception testing the decision not to procreate will always be based on risks backed by greater or lesser scientific certainty, higher or lower probabilities, whereas decisions made on the basis of prenatal diagnosis are based on hard fact –the condition has already been produced in the fetus and is detectable– making the terms of the comparison unequal. But it is equally true that the decision in the former case is limited to avoiding procreation, while the latter requires abortion.

The geneticist Marjorie Shaw, clearly advocating the former course, has called for governments to pursue policies to prevent genetic risks by checking reproduction in families that are informed of potential genetic disorders. Foregoing procreation when a risk is known seems preferable to aborting the fruit of procreation after the harm is done.

In any event, considerable benefit could be attained from the availability of a genetic test allowing couples contemplating child-

bearing to know the risks run by their future children. The advantages of such a genetic test could make it acceptable.

This statement leads me to the next item of ethical and legal reflection. Should the test be obligatory or voluntary? Can future spouses be required to submit to a genetic examination prior to marrying, or should they be free to decide whether or not to undergo the test?

Moreover, attention must be paid to the breadth and depth of the test and to the scope of its disclosure. Should the test cover the entire genome or be limited to the parts that can affect offspring? Should the result be known only by each of the interested parties? Can –or better yet, should– the other spouse be informed of the results? Should the information be furnished to the person presiding over the wedding? Should legal capacity to marry depend on the results? Should certain results bar a person from entering into wedlock?

Genetic testing and family law

Before continuing, I must make two important observations.

The first is that genetic testing can be effectively used within Family Law for decisions other than those relating to procreation. Second, our positive law contemplates some of these scientific developments and has incorporated them into current legislation and judicial practice.

As for the first point, court rulings on patria potestas, its suspension or privation, or on child custody and care, are to be made for the benefit of the child. Clearly, the current assumption is that such decisions must be based on knowledge of the progenitors and descendants so that the court's discretion can be based on mature reflection on the relevant facts. Such knowledge is often difficult and complicated to attain and the Judge is consequently authorized to hear the findings of experts (section 92 in fine Civil Code), usually limited to psychologists. The detection of greater or lesser propensities to serious behavioural disorders or mental disease, for example, or even the prospect of other physical ailments which might materially hinder child-care, could no doubt be of pivotal importance and utility for court decisions regarding patria potestas or child custody.

In adoption cases, genetic tests of the adoptive parents could reveal conditions and circumstances of great influence on any

evaluation of their appropriateness as parents. However, the risk exists in adoptions that such tests be applied not to the adoptive parents but to the children awaiting adoption in public homes, and that the results be revealed to the potential parents, who would no doubt reject children diagnosed as being at risk. A child vulnerable to defects or disease, or with a predisposition to disorderly behaviour, would be unlikely to be adopted, producing inadmissible discriminatory results.

As for the second aspect, Family Law reforms of 1981 included the admissibility of paternity and maternity investigation «by means of any kind of tests, including biological ones» (Civil Code section 127). Paternity tests have in fact been regularly practiced since and, in step with the advance in genetics, have become almost completely reliable both as to negative results excluding paternity and positive ones establishing it.

The most serious problem arises –in cases of paternity disputes as with those involving child custody or adoption decisions– when we examine whether these tests can be made obligatory. And we have yet to establish the consequences of refusing to comply with such an obligation where it exists. For if there is no means of enforcing the testing obligation or for punishing refusal, mere declaration of obligation becomes purely illusory.

The doctrine which has emerged in Spanish law, after some initial vacillating, is that refusal to submit to filiation tests by the doubtful father or mother, usually the former, does not constitute a *ficta confessio* (tacit admission) of paternity/maternity, but does represent a valuable indication which in the company of other evidence allows a presumption of progenitorship.

In the process of reaching these conclusions, Spanish legal doctrine has reaffirmed several principles. The first is that when any of these questions involving minors are examined, the principle of benefiting the child must prevail, at least in large part, over other general principles and fundamental rights.

Secondly, the principle has been established that the right to privacy, under which some defendant progenitors have sought protection for refusing to undergo paternity tests, is overridden by the right of the child to know his or her origin. Presumed progenitors in some paternity suits have invoked the right not to reveal their genome, which as genomic knowledge advances includes ever more fundamental and reserved aspects, stating that such right can be infringed upon by paternity searches. But these arguments have not met with success.

I should also include here the criminal trials use of genetic identification tests, not only in relation to sex crimes but with all others in which there exist traces of blood or other human body substances such as skin or hair. Identification is becoming of pivotal importance in cases of missing or kidnapped children, whether in normal times or as the result of war or revolution.

An example of this latter application is Argentina's National Bank of Genetic Information, created in 1985. This agency offers families of missing children the possibility of determining the identity of their lost relatives by comparing their genetic information with that of family members.

A similar purpose is at work in Dr Garrido Lestache's proposals –approved though not yet enacted– for identifying newborn babies in order to avoid kidnappings and accidental maternity-ward switches. Genetic tests could be used for this purpose and offer more precision than fingerprints.

As genetic science moves ahead, the individual's right to limit possible intrusions into his or her privacy could be affected by the development of more effective, cheaper and accurate methods. It could be a matter of a simple test performed on a newborn child as Doroth Nelkin has alerted [2]. The American Society for Human Genetics has considered proposals for taking umbilical cord samples from infants at birth and keeping their DNA, which would imply the possibility of storing genetic information for all newborns. According to the aforementioned author, in the United States there are biotechnology companies that advertise their data archives and urge that people deposit DNA samples of their family members for analysis and safekeeping. What is more, it is predicted that in the future most persons will have their genetic profiles stored in some place, as a preliminary step to the great benefits all will derive from these advances.

Of course the prospect of such a register existing brings to mind the possible –certain– desire of the government, and countless agencies and citizens, to have access to its contents. These include not only insurance companies and prospective employers of the people in question (to name the traditionally two most controversial areas when discussing access to genomic information), but also, and perhaps even more so, immigration or traffic authorities, organ transplant agencies, child adoption institutions, the military, banks and other lending institutions, scholarship grantors or other similar benefactors, professional sports teams, and, even, possible future sexual partners.

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[2] «The Social Power of Genetic Information», *The Code of Codes*, op cit, p. 187.

Genetic testing and matrimony

Nancy Wexler expresses a widespread view in the United States when she asserts that genetic testing should be a mandatory requirement for marriage [3]. Procreation decisions by the spouses –or future spouses– which are today conditioned by economic, employment and social factors, or simply by relatively unthinking decisions, could be supported by important health considerations. Furthermore, certain decisions which today are adopted during the pregnancy in view of prenatal analyses could be taken beforehand. Persons opposed to abortion could attain genetic information prior to marrying or before having to face procreation decisions.

There are several different approaches to pre-marital genetic screening and its possible consequences for future offspring. The first is to make it absolutely voluntary, with each person free to decide whether the results are to be disclosed, fully, partly, or not at all, to his or her partner. This system poses no particular problems other than the assistance which the couple might need in evaluating the results or in psychologicaly confronting the existence or prediction of a disease or defect.

The other alternatives consist of making testing mandatory. It is first necessary to establish which tests are to be required and whether they should be as broad-ranging as scientifically possible or, conversely, limited to offspring-affecting aspects. In the first, broad testing allows each of the future spouses to acquire greater somatic-cell information and, therefore, insight into their predisposition to determined disorders and diseases or conducts. In the second, testing is confined to elements which could determine malformations, diseases, predispositions or behaviour in the descendants and the information acquired concerns the existence, and evaluation of such disorders.

Making genetic tests mandatory also raises the issue of disclosure of the results. There are several options. One, the obligation of prompt disclosure of test results to, and only to, one's partner. Two, the obligation to reveal the results to the person who authorizes or presides the matrimony. And three, the absence of any obligation to disclose the results, with the interested party holding the information for him or herself.

Thus, we must analyze the problems involved in genetic testing requirements according to whether they are mandatory, the

[3] Nancy Wexler: «Clairvoyance and Caution: Repercussions from the Human Genome Project», *The Code of Codes*, op cit, p. 234.

scope of their disclosure, and the possible ramifications of the results.

Mandatory pre-marital genetic testing

We must remember that according to the II Valencia Declaration, nobody can be subjected to genetic analysis without their knowledge, but that this prohibition does not rule out the possibility of mandatory testing.

Obligatory submission to these tests, however, does raise a number of problems. Even in the most favourable case, where the result is only known to the medical professional who conducts the test and the interested party, the very existence and record of the DNA analysis prompts certain fears. There is the suspicion, or doubt at least, that for some reason or another the analysis might be disclosed to institutional or individual third parties. From the simple breach of the confidentiality obligation by the report's custodians, to, for example, the possibility of a criminal court order, there are many ways in which an individual's intimate genomic knowledge could become known to others not of his choosing.

There is also the fear of the person who undergoes genetic testing on learning the results of such an incalculably significant test. In the medical world there is a permanent conflict between the moral obligation, convenience or, to a lesser extent, appropriateness of whether or not to reveal a disease, its breadth and foreseeable consequences, to the afflicted patient. The principle of individual autonomy argues in favour of a person's right to know his or her real condition as the basis for making decisions. Reasons of a psychological nature, given possible harmful reactions to such knowledge, or the desire to avoid unnecessary suffering can be cited as grounds for maintaining the results secret. Perhaps the results should be disclosed to close relatives. A judicious solution may possibly require case-by-case analysis, carefully weighing maturity and psychological stability of the individual involved.

Two contradictory attitudes compete within the potential patient: the desire to know and the fear of knowing. They are the correlative and contraposed rights to know and to not know.

Since the earliest times, humanity has exalted those persons displaying a capacity to read the future. Oracles, augurs, soothsayers and fortune-tellers, readers of coffee grinds and cards, have been widely called upon to reveal the future in all ages and in all lands. Today they are still important amongst sceptics and believers.

Astrologers and their horoscopes are a fixture in our mass media. Zodiac and Chinese signs appear with one aim: to predict our future and reveal our individuality, both as regards the imponderables of fate, fortune, destiny, and, very especially, health, the evolution of our intellect, the expression of our virtues and of our defects.

Man wishes to learn his future and to know it. In reality, he seeks to know the good and, perhaps, the avoidable and solvable, and is loath to learn of harm, ill-fate, and the inevitable.

Many benefits can be obtained by an individual from knowing as much about his or her genome as scientifically practicable at each point in time. In particuliar, the larger the number of gene therapies available for curing ills, the greater the beneficial effect of early risk-detection. But information as to risks should be seen as tied in not only with the possibility of curing disorders, but also with the capacity to adopt informed decisions on the questions before us, that is, sexual relations and procreation.

In light of the above reasoning, obligatory genetic testing could be justified when the issue is one of protecting descendants and avoiding the transmission of serious deficiencies or disease. It may be less appropriate, however, when used as a means of knowing characteristics or conditions evaluated as beneficial on the basis of racist, or simply capricious or arbitrary, criteria.

In any case, the appropriateness of mandatory genetic tests may depend on the extent of their content and the scope of their disclosure.

Disclosure

The already mentioned II Valencia Declaration states that information obtained from genetic tests must not be communicated to anyone without their owner's permission.

Nevertheless, as John Fletcher has said, «confidentiality is a fundamental norm, but not absolute in medicine and in medical genetics. If the patient refuses to reveal the possible existence of an evident risk for his family, the imperative of avoiding possible harm to other persons limits the doctor or counsellor's duty of confidentiality». That is the case, for example, with epidemics or plagues, where the general good prevails over the person's interest.

As is often the case in difficult issues, several principles apply and can come into conflict, making it difficult to clearly demarcate the different areas they protect. The crucial step is to set down the criteria for determining prevalence among different essential principles.

Divulging such intimate and personal information as the results of genetic tests infringes upon the essential right to privacy. However, as we have seen when studying biological filiation tests, this principle can be overridden by the child's right to know his ascendancy, which is considered a higher good. This psychosociological right to know one's origin is also undeniably associated with the essential right to health and to benefit from scientific advances, insofar as information on one's ancestors increases awareness of susceptibility to certain disorders and diseases and can aid in their cure.

Hence, if the existence of the right to know one's progenitors justifies setting aside the protection of privacy in biological testings, the right to privacy can in the same way be considered subordinate to improved health or absence of defects and handicaps in offspring.

Defining the boundary between competing fundamental rights is of course highly conditioned by the intended degree of disclosure of the genetic tests. To the extent that information is divulged for the sole purpose of avoiding physical and mental harm to descendants, disclosure may be justified by the principles which protect the latter. The right of the fetus of today and the man of tomorrow to health and physical and mental wellbeing is unquestionable.

When the possibility exists of this information being used for other, less-protected purposes, the right to privacy again regains its full force and clashes with those other purposes. The contending interests then have to be weighed to determine which should prevail.

Different authors who regard onfidentiality as an unquestionable basic principle but admit exceptions have suggested that diagnostic testing of newborns could be made obligatory only when treatments are available to assist victims of genetic disorders. Others believe that clinically significant genetic information should be disclosed to the person involved and to his or her family. Some feel that only those results with effects on health should be made known. Eric Lander has said that «with the growing acceptance of DNA identification and growing interest in DNA data banks, it is reasonable to wonder whether our DNA could become our "social security number"». And later continues: «So-

me authorities have proposed DNA-typing of all newborns to facilitate identification of a child who has been kidnapped and later found. Once initiated, typing of newborns could lead to the creation of a national DNA data bank, specifying not only each individual's identifying mosaic but his medical and possibly behavioural characteristics as well» [4].

Effects

In this analysis a pivotal role is played by the matrimony-related aim of the genetic tests performed. If the purpose is to prohibit marriage by persons unable to meet a standard of absence of offspring risk, the results would necessarily have to be revealed to the civil officer or registry judge so that the union could be blocked, as is currently the case with prenuptial medical certificates in some legislations.

On the other hand, if the pursued aim is to aid the couple –both members– in their decision to marry and/or have children, the genetic information would have to be revealed to the other spouse. They could thus together, with full knowledge of their respective genetic identities, of their most basic characteristics, and aware of their own genome and that of their partner, freely decide whether to accept or reject the risks to their offspring.

In the first assumption, that is, when the aim is to place legal conditions on wedlock when the tested DNA suggests the children would run genetic risks, the possible clash with certain fundamental principles must be weighed. There is on the one hand the right not to be discriminated against for reasons of health or disability, which could be invoked by a person whose genome carries the possibility of hereditary transmission of disease, malformation or behavioural abnormalities. Such an individual could find himself discriminated against as to matrimonial and/or reproductive possibilities.

The right to equality could thus be affected, along with that of entering into marriage, founding a family and procreating. However, these rights are undoubtedly limited by the right to equality protecting citizens against discrimination which has no objective reason or logical or necessary basis. Does a person carrying the seed of a serious illness or malformation, the transmission of which to his or her children is highly likely, have an equal right

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[4] Eric Lander: «DNA fingerprinting: Science, Law and the Ultimate Identifier», *The Code of Codes*, op cit, p. 209. This quotation has been translated from the Spanish version.

to procreate as do other persons? Does the right of the future person to be born without defects prevail when a high risk of inheriting such disabilities exists? Is this improper discrimination for reasons of health?

There are those who contend the fundamental importance of protecting the freedom of parents to decide the birth or not of a baby in whom prenatal tests have detected deficiencies or defects. The defence of this freedom, however, is conditioned by religious and moral positions on abortion. A couple's freedom to decide whether or not to procreate is without the slighest doubt not the same as the freedom to decide on continuing or ending a pregnancy. Ethical considerations must be viewed differently in the exercise of a couple's free procreative will when genetic testing has revealed the risk that the fetus will suffer serious genetic defects. The risk's likelihood should be weighed in the decision-making process.

It should not be forgotten that mental patients are discriminated against when they are kept in psychiatric centres against their will. Although done with judicial guarantees, they are deprived of their freedom. Nor should it be forgotten that sterilizations are performed on human beings. They are done under court supervision, but the persons are nevertheless deprived of their reproductive capacity and right to procreate for medical or even demographic reasons.

Can the capacity to enter into matrimony, or to procreate, be somehow limited or denied by virtue of the results of genetic tests?

In order for the limitation or prohibition to be effective, the results would have to be divulged to the other partner, the person authorizing the marriage, or both. And this would have to be done without the consent or against the will of the tested person or tested couple.

There is also the option of requiring candidates for marriage to undergo genetic testing but to divulge the findings only to the individuals themselves –each person only knowing his or her own results– thus leaving reproduction decisions to their conscience, to their respective sense of «responsible parenthood» in the light of the risks detected. This would be to adapt the current pre-wedding certificate system in France and Luxembourg to genetic testing. The testing officer would formally certify that the tests were conducted and the results disclosed to the interested party. The couple would qualify to marry by presenting the certificate. Such a system would ensure that the tests are mandatory and that they serve as a means to detect genetic abnormalities. It

could be effective in preventing and curing genetic diseases without violating the confidentiality of the results. Therapeutic and procreative decisions and the waiver of the right to privacy would be left to the conscience and will of the persons involved.

In any case, under this system the person would be forced to carry through that genetic introspection of unknown ramifications. It would be required that the individual– and perhaps only that individual– know his or her shortcomings, potential infirmities, behavioural leanings and so many other peculiarities. The right not to know would be contravened and, as knowledge of the genome will necessarily much antedate gene therapy, adverse test results could have dire, demoralizing consequences for a tested person having to face as yet uncurable ills.

On the other hand, such knowledge should be viewed as perhaps beneficial to descendants saved from the transmission and generation-to-generation perpetuation of lethal or highly destructive seeds.

It is once more necessary to weigh contradictory principles, contraposed risks and contending benefits. Again, norms must be adopted whose application enhances the advantages and diminishes harm.

What turns out to be clearer is that it is always possible to educate the public about genetic testing and promote its practice without resorting to the terrible risk of the state's invasion of the private sphere in the form of legal obligations and prohibitions that hinder the development of individual freedom.

But time is fair and just, and respects the essential human rights which we as jurists must defend, recognition and confirmation of the individual's option to know and capacity to freely adopt mating and reproduction decisions.

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ETHICAL ASPECTS OF THE LEGAL PROBLEM OF CONFIDENTIALITY

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1. The logical relation between ethical and legal codification in general is one of non-contradiction: If a given piece of legislation –be it already effective or «sub judice»– contradicts moral principles validated by ethical reasoning and/or constitutional rights, then the law in question has to be changed. This, of course, is a logical relation of the «necessary condition»-type; moral principles and ethical reasoning do not constitute sufficient conditions for legal codifications.

2. The main legal problem of confidentiality with respect to genetic information could be boiled down to the following alternative: individual right to (genetic) privacy versus public right to self-protection, both against criminality and against diseases. Or –to put it differently– the right to «informational self-determination», as it has in the FRG resulted from the general personality-right (Art. 2 Abs. 2 GG) in connection with the human dignity right (Art. 1 Abs. 1 GG) limited by the very same rights of other individuals and/or the public only. In out case: If exerting the right to informational self-determination of and individual p_1 should conflict with the exertion of the right of informational self-determination of another individual p_2 or of the set $p_1..n$, then the right of the individual p_1 must be confined to such a degree that in exer-

tion doesn't conflict with the exertion of the respective rights of the others.

3. As far as genetic data of individual human beings are concerned it is helpful to distinguish between «strictly private personal genetic data» and «publicly accessible personal genetic data» (Zimmerli 1990) [1]: Although we might in a given situation not be capable of technically seperate these two types of data it makes –for analytical purposes– good sense to distinguish between the individual set of genetic data constituting (or rather defining) the individual physical existence and appearance of and individual as a particular person in the legal sense, and information about the generally valid principles of the localization of functions and the coordination of one-to-one, or one-to-many and many-to-one relations between genes and gene expressions.

4. Within the context of research the individuals have –according, of course, to the principle of informed consent– waived their right to informational self-determination to the extent that the institution in charge of performing the research is able to guarantee confidentiality with respect to the strictly private personal genetic data. Within the context of medical prevention the same is true. Talking about diagnostic application of gene-biological tools it must even be considered whether the individual person in question is morally obliged to waive even his/her right to confidentiality. Within the context of crime prevention and/or criminal proceedings it goes without saying that the subject in question has lost his/her claim to self-determination with respect to strictly private personal genetic data. He/she nevertheless still is in possession of a claim to confidentiality as far as the procedures in the criminal action are concerned.

5. Whereas the problems discussed so far are mainly a question of legislation already existing in most of the EC countries, the main technical question brings about some problems not yet solved in the legal systems considered so far. Acquiring and handline of the genetic data with respect to the human genome requires a hybridization of molecular biology and data processing procedures. As everybody knows it is impossible to design a waterproof data protection system. Therefore it is necessary that the legislator steps in at this point with laws penalizing the abuse of strictly private personal genetic data. The main problem nevertheless remains untouched: how to technicaly keep the different possibilities of abuse under surveillance without violating higher order constitutional rights.

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[1] Zimmerli, W.Ch. 1990, «Who has the right to know the genetic constitution of a particular person?», in *Human Genetic Information: Science, Law and Ethics*. Ciba Foundation Symposium 149, Chichester, 93-102.

ROUND TABLE

ROUND TABLE

Alexander M. Capron. I come from a state identified by Professor Edgar as the origin of all things novel and questionable. My question is for Professor Edgar. I wanted him to expand upon and perhaps explain the suggestion of the obligation for disclosure of information by a family member to other family members. The specific example that he gave was a potential spouse, one to the other. But if it exists in that context, I suppose one might argue that its exists among blood relatives as well. He attempted to justify that by reference to the obligation recognized by some courts in the United States of a physician to provide information to parents about the genetic or other risks that exist with a fetus *in utero,* so that the parents may make an informed decision about carrying the pregnancy to term. In my view, the analogy is not apt. There is no basis for looking at the obligation that a professional has and saying that the same obligation governs the disclosure of information between people whose relationship is not that of physician and patient. And specifically, madame Chairman, it seems to me that in the area which he describes of prenatal information, the issue is whether or not there could be a wrong in failing to allow someone to have information to abort a child and whether, when that had not been done and a child was born, there was a wrong that the law could compensate. But there was never any initial question about the obligation of the physician to provide information. That was the groundwork on which that was based. And I think to make an analogy to the spousal situation or to the obligations of a cousin to tell another cousin that a genetic factor had been found, or whatever, is to leap over the question which should concern us: Is there a duty in the first place? And so, by looking at the wrongful birth cases, as they are called, and the wrongful life cases, one cannot make an analogy, because those begin with an understanding that there is a duty, and ask only the question: Is there a compensation when that duty is violated?

Answer. Part of the problem in trying to compress is that one risks mis-speaking, and in my example of late onset disease, I mis-spoke. What I intended to refer, and I think what Alex Capron was kind enough not to catch me up on, is the situation in which the spouse has some fear that a child of the marriage will be genetically handicapped. As to Alex's failure to see the way in which the law might evolve, all I can say is I disagree. There are United States cases, for example, holding men liable when they misrepresent to women (in at least one case I believe, in a marriage context) when they are sterile. So that is a situation in which the law has held compensable the misrepresentation of information in an intimate context. I do not think the law will have any trouble in saying that it is tortious to misrepresent. Then the question is will the law have a difficulty in the context of a situation where no formal representation is made, of saying, if you know this, you have a duty to make the representation. In the context of the physician who is at risk of being infected with HIV, there was no misrepresentation. There was simply a failure on the patient's part to tell that which the court and jury, looking under standards of what is and what is not reasonable, said: yes, you have a duty to tell under those circumstances. That is the way I see the law evolving, at least potentially. I may add a comment to that as well, I do not think that courts will likely look to the bioethics literature in deciding how or whether that issue should be decided.

Question (Rafael Velázquez). I would like to raise two very specific questions. The first is, in the face of the processing, analysis, access and dissemination of genetic data results, what balance should there be between the right to privacy, to protect one's health, and the right to research and the principle of the free circulation of information as formulated by the OECD? And the second question is the following: Given that genetic data are data which are automatically processed, wouldn't they be possibly covered by Council of Europe Convention 108, the Spanish Organic Act on the Regulation of Automated Data Processing, and, once it is in effect, by the Draft Council Directive on Data Protection and Systems Security? Thank you very much.

Question (Francisco Lledó). I will be very brief. The truth is that I would like to ask a great many questions, but I do not know where my receiver is. Anyway, I will try to be very succinct and summarize my paper. This critical decalogue of ethical axiologies and apothegms, in reality, has left us jurists in a bad way, but what is missing for me –I do not know if out of omission or otherwise– is a question I consider of prime importance. And that is: In what way can we specify where we may find the foundations and ethical assessment of the criteria that should govern law and justice? Since I do not merely want to ask, but to answer –I do

not know if I will receive a reply– I believe that, in my view, they should be looked for in what we call the general principles of law. General principles formulated not as heuristic rules, but as general principles from a social and general, objective estimation, not one particularized for each specific case. I think this is an important starting point. And, getting down to specifics, I would say that the principal constitutional principle would be the one referred to by Professor Peces Barba –and I am in agreement with him perhaps only on this and a few other points– the constitutional principle of respect for human dignity, the linking and protecting gateway to all the other fundamental rights.

Another important question which has also been cited here is that of public ethics. I do not know where to locate the groundwork or foundational parameters for the legitimation of this public ethics, that is, the commonly accepted objective values. I do not know; perhaps within those general principles of law I referred to earlier. And I will end with this question, addressed perhaps to all of you. Within a «scientificist» utilitarian conception, doesn't this genetic manipulation pose a risk of a genetic determinism and reductionism, of a scientific colonialism, in which the developed powers hold the greatest weight and the less developed countries, to some extent, I do not mean to say that they tail the former, but that they become technically colonized? With this predictive genetics are we not running the risk of individuals becoming life-long patients?

Fernando Garrido Falla. I believe, for my part, that only your second question, as to the protection of computerized data relative to a person's genetic makeup, corresponds to me. Indeed, although I was not given enough time to properly explain it, these cases are of course covered by Act 5/1992, where, first of all, it is required that in order to gather such data the person from whom they are requested must be informed as to the use that will be made of the data. Secondly, the Act says that, in the case of certain types of data, the person of course has the right not to reply. What is more, there is even a small loophole (and I think I mentioned this), a small exception which the Act allows for cases of public interest, etc. I do not know whether or not it has been challenged as unconstitutional, but I have been informed that there has been discussion of such a step and that a constitutional challenge has been proposed to this small door left ajar by the Act. As for the other questions, I think I am not the most appropriate person to answer them.

Bartha M. Knoppers. Two very brief comments on specific legal questions. One as to the possibility of heightened legal duties between spouses and the other with regard to whether constitutional law already contains the general principles necessary to

protect genetic privacy. Surely if a physician bound usually by codes of ethics, but also by law, has a duty to reply to and answer questions concerning genetic information, even prior to conception, one can argue, at least under civil law principles, that between married individual –leaving common law unions aside– there is a duty flowing from the fact of marriage, the duty of succour, care and assistance. Persons who stand in a special relationship, such as spouses, or family members by blood, going in ascendant and descendant order, already have under law certain heightened obligations, certain special duties. And I think the framework could be found even within current family law constructs to extend those kinds of duties beyond alimentary or medical treatment or other obligations to include the communication of information as part of that care, succour and assistance.

As far as constitutional law goes, I would agree with you that the principles already enunciated in most constitutions, as well as in international texts, contain the bases for the construction of challenging legislation or the need for a redefinition of certain concepts, such as liberty, definitely dignity, and certainly privacy for those countries which have specific references to privacy. Each constitution, as well as international texts, also contains express clauses that allow states to interfere or limit the free and total expression of those rights according to what is necessary in a free and democratic society. I think that is where the public interest, towards future generation as well as to the sharing and protection of genetic information in this present generation, can come in any possible legislation.

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This work is the formal result of the International Workshop on *The Human Genome Project: Legal Aspects* (Bilbao, 1993), organized by Fundación BBV in collaboration with the Provincial Deputation of Bizkaia. Its central aim is to lay down legal criteria for addressing the relations between law and the genome project. Both the specialist and the non-jurist alike, each according to their needs, can find in these volumes a clear and multi-sided perspective on the state of these questions in Spain and abroad.

These pages offer the reader an adequate legal and scientific introduction to the field, as well as answers to the fundamental questions raised by this challenge of world science. Subjects such as freedom and genes, privacy, and the culpability principle are extensively analyzed and discussed. Specific issues relating to patents, insurance and employment relations are likewise covered, without neglecting sensitive problems concerning criminal identification and limits on genetic manipulation.

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