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The Human Genome

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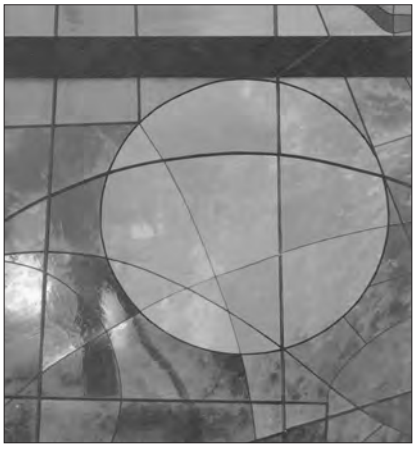

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Saturday 19 November

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La Casina Pio IV in Vaticano.
Guida storica e iconografica
Pontificia Accademia delle Scienze
Città del Vaticano, 2005

ADDRESS OF HOMAGE TO THE HOLY FATHER

In the Apostolic Letter 'Motu Proprio', '*Dolentium Hominum*', which instituted this Pontifical Council for Health Pastoral Care, we are asked 'to promote and intensify necessary activities of study for proposals and examination' (n. 5) in relation to the specific problems of the health care service within the specific context of the true good of man. Amongst these problems the above-mentioned Apostolic Letter mentions, and I quote, 'The new frontiers that are opened up by the advances of science and its possible technical and therapeutic applications, bear upon the most delicate areas of life at its very sources and its deepest meaning' (n. 3)

Specifically in order to attempt a detailed response to the questions of the sources of life and health, within the Pontifical Council for Health Pastoral Care, having received the approval of your beloved predecessor, His Holiness John Paul II, we chose as the subject of our twentieth international conference 'the human genome'. Speakers of great expertise from seventeen countries and participants from eighty-two countries met together to give concrete expression to this proposal.

Our task is to place current wonderful genetics side by side with the Gospel in order to illuminate with the Word of God the most delicate spheres of life at its very sources. In this illumination, your words, Your Holiness, will be our guide that will lead us towards the true good of man in the very source of health.

Holy Father, I have the honour to offer you the affection and the adherence of our speakers and participants – Cardinals, Bishops, priests, men and women religious, and secular people, who with their scientific, philosophical and theological knowledge and expertise brought about this conference.

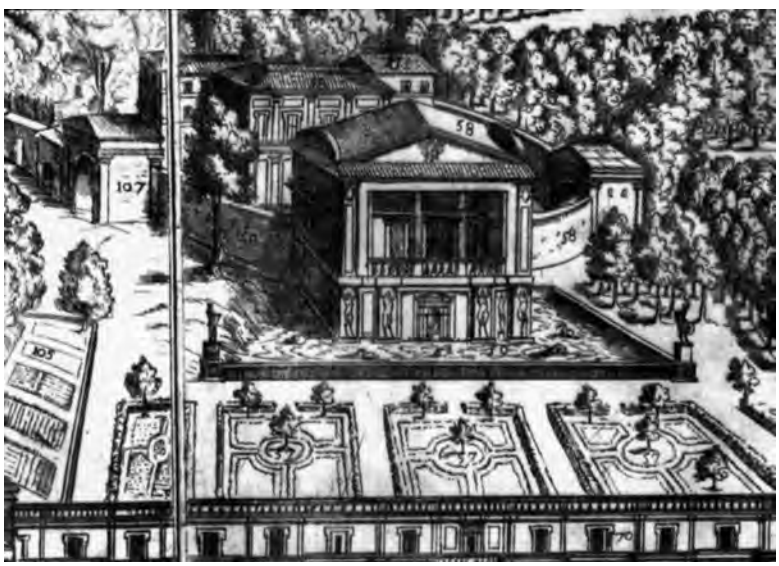
We are all very happy to have gained from the presence of the personal delegate of His Holiness Alexis II, of the Patriarchate of Moscow, and of the Metropolitan Nicolaos, a member of the Holy Synod and delegate of the Greek Orthodox Church.

Now, Holy Father, we have arrived at the culminating point of our conference of being received by Your Holiness and being able to have the privilege of hearing your authoritative words which will constitute the definitive guide for our work.

Very many thanks, Holy Father; in our joy to be in your presence we prepare ourselves to listen to you with attention, humility and devotion.

Vatican City, 19 November 2005.

H. Em. Cardinal JAVIER LOZANO BARRAGÁN
President of the Pontifical Council
for Health Pastoral Care,
the Holy See



ADDRESS OF HIS HOLINESS BENEDICT XVI

Every New Scientific Discovery Will Serve the Integral Good of the Person, with Constant Respect for His or Her Dignity

Your Eminence,
Venerable Brothers in the Episcopate and in the Priesthood,
Distinguished Ladies and Gentlemen,

I address my cordial greeting to you all, with a special thought of gratitude to Cardinal Javier Lozano Barragán for the kind greeting he has expressed on behalf of those present.

I offer a special greeting to the Bishops and priests who are taking part in this Conference as well as the speakers, who have certainly made a highly qualified contribution to the problems addressed in these days: their reflections and suggestions will be the subject of an attentive evaluation by the competent ecclesial bodies.

Placing myself in the pastoral perspective proper to the Pontifical Council that has sponsored this Conference, I would like to point out that today, especially in the area of breakthroughs in medical science, the Church is being given a further possibility of carrying out the precious task of enlightening consciences, in order to ensure that every new scientific discovery will serve the integral good of the person, with constant respect for his or her dignity.

In underlining the importance of this pastoral task, I would like first of all to say a word of encouragement to those in charge of promoting it.

The contemporary world is marked by the process of secularization. Through complex cultural and social events, it has not only claimed a just autonomy for science and the organization of society, but has all too often also obliterated the link between temporal realities and their Creator, even to the point of neglecting to safeguard the transcendent dignity of human beings and respect for human life itself.

Today, however, secularization in the form of radical secularism no longer satisfies the more aware and alert minds. This means that possible and perhaps new spaces are opening up for a profitable dialogue with society and not only with the faithful, especially on important themes such as those relating to life.

This is possible because, in peoples with a long Christian tradition, there are still seeds of humanism which the disputes of nihilistic philosophy have not yet reached. Indeed, these seeds tend to germinate more vigorously, the more serious the challenges become.

Believers, moreover, know well that the Gospel is in an intrinsic harmony with the values engraved in human nature. Thus, God's image is deeply impressed in the soul of the human being, the voice of whose conscience it is far from easy to silence.

With the Parable of the Sower, Jesus in the Gospel reminds us that there is always good ground on which the seed may fall, spring up and bear fruit. Even people who no longer claim to be members of the Church or even those who have lost the light of faith, nonetheless remain attentive to the human values and positive contributions that the Gospel can make to the good of the individual and of society.

It is particularly easy to become aware of this by reflecting on the topic of your Conference: the people of our time, whose sensitivity, moreover, has been heightened by the terrible events that have clouded the 20th century and the beginning of the 21st, easily understand that human dignity cannot be identified with the genes of the human being's DNA and is not diminished by the possible presence of physical differences or genetic defects.

The principle of "non-discrimination" on the basis of physical or genetic factors has deeply penetrated consciences and is formally spelled out in the charters of human rights. The truest foundation of this principle lies in the dignity inherent in every human person because he or she is created in the image and likeness of God (cf. Gn 1: 26).

What is more, a serene analysis of scientific data leads to a recognition of the presence of this dignity in every phase of human life, starting from the very moment of conception. The Church proclaims and proposes this truth not only with the authority of the Gospel, but also with the power that derives from reason. This is precisely why she

feels duty bound to appeal to every person of good will in the certainty that the acceptance of these truths cannot but benefit individuals and society.

Indeed, it is necessary to preserve ourselves from the risks of a science and technology that claim total autonomy from the moral norms inscribed in the nature of the human being.

There are many professional bodies and academies in the Church that are qualified to evaluate innovations in the scientific environment, particularly in the world of biomedicine; then there are doctrinal bodies specifically designated to define the moral values to be safeguarded and to formulate norms required for their effective protection; lastly, there are pastoral Dicasteries, such as the Pontifical Council for Health Pastoral Care, whose task is to ensure that the Church's pastoral presence is effective.

This third task is not only invaluable with regard to an ever more adeguate humanization of medicine, but also in order to guarantee a prompt response to the expectations by each individual of effective spiritual assistance.

Consequently, it is necessary to give pastoral health care a new impetus. This implies renewal and the deepening of the pastoral proposal itself. It should take into account the growing mass of knowledge spread by the media and the higher standard of education of those they target.

We cannot ignore the fact that more and more frequently, not only legislators but citizens too are called to express their thoughts on problems that can be described as scientific and difficult. If they lack an adequate education, indeed, if their consciences are inadequately formed, false values or deviant information can easily prevail in the guidance of public opinion.

Updating the training of pastors and educators to enable them to take on their own responsibilities in conformity with their faith, and at the same time in a respectful and loyal dialogue with non-believers, is the indispensable task of any up-to-date pastoral health care. Today, especially in the field of the applications of genetics, families can lack adequate information and have difficulty in preserving the moral autonomy they need to stay faithful to their own life choices.

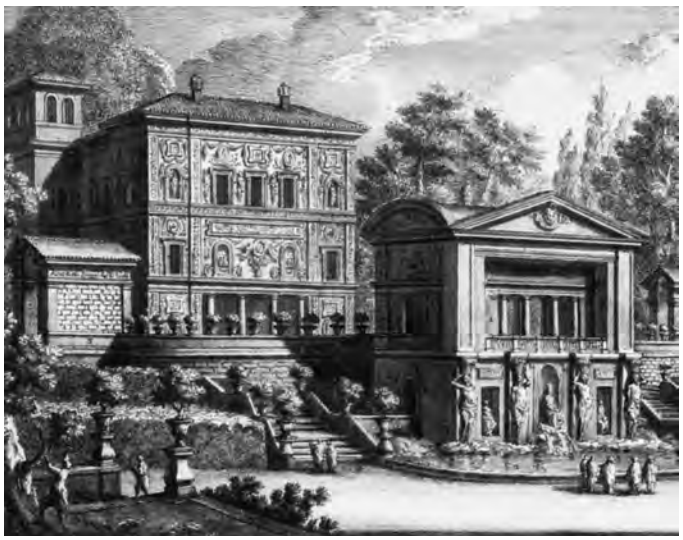
In this sector, therefore, a deeper and more enlightened formation of consciences is necessary. Today's scientific discoveries affect family life, involving families in unexpected and sensitive decisions that require responsible treatment. Pastoral work in the field of health care thus needs properly trained and competent advisers.

This gives some idea of the complex and demanding management needed in this area today. In the face of these growing needs in pastoral care, as the Church continues to trust in the light of the Gospel and the power of Grace, she urges those responsible to study a proper methodology in order to help individuals, families and society, combining faithfulness and dialogue, theological study and the ability for mediation.

In this, she sets great store especially by the contribution of all, such as you who are gathered here to take part in this International Conference and who have at heart the fundamental values that support human coexistence. I gladly take this opportunity to express to you all my grateful appreciation for your contribution in a sector so important for the future of humanity.

With these sentiments, I invoke from the Lord an abundance of enlightenment on your work, and as a testimony of my esteem and affection, I impart a special Blessing to you all.

Vatican City, 19 november 2005



The Human Genome

PROLUSION

Thursday
17
November

JAVIER LOZANO BARRAGÁN

Life: a Gift of Love

Reflecting on the human genome, and by way of a brief introduction to our international conference, I will try to present some contributions on life as a gift of love, hoping that these observations will be useful in contextualising our study in the light of the Message of Revelation.

My paper will address the following points:

I. Life. The Rudiments of Biogenetics
The beginning of human life

II. Life. Movement
Organicity-Finality
Internal unity
External unity
The denial of distinction

III. Life as Opposition
Various oppositions
Contradiction
Contrariety

IV. The Trinitarian Christian Life
The Incarnation
Contradiction and contrariety

I. Life. The Rudiments of Biogenetics

Allow me to refer to certain scientific foundations regarding the origin of human life. It may seem ridiculous to do this in front of scientists of such a high level, such as those who are taking part in this international conference. I will do this, however, and I apologise to you for doing so and ask for your understanding, only because they will be useful to me as elementary facts from which I would like to begin my analysis of life as a gift of love.

The beginning of human life

Human life begins in a cell that is formed of a cellular membrane, the cytoplasm, the nuclear membrane and the nucleus. In the cytoplasm there is a series of structures with various functions such as the ribosomes, where the proteins are synthesised. These are seen as the primary product of genetic activity. The nuclear membrane separates the cytoplasm from the nucleus, within which there are the chromosomes, in which are deposited the DNA and the genes which, in their turn, are located in the DNA. Human life takes origin from the chromosomes through the energy of the DNA with its genes. How does all this take place?

The initial elements of human life:

1. The actors

There are five actors, namely: the chromosomes, of which there are twenty-three pairs and thus forty-six in total; the DNA (deoxyribonucleic acid), where there are the chromosomes, which wraps them together rather like a helix with one and three quarter turns; the RNA (ribonucleic acid), which acts as a messenger and a transporter of DNA: the mDNA and the tDNA; the genes – a minimal portion of the DNA which determines life and which thus must be ordered by threesomes together – which are called 'triplets'; and the proteins, which when they have a metabolism function are called 'enzymes', which are twenty amino acids ordered by the DNA. The function of the genes is explained below.

Of the twenty-three pairs of human chromosomes, twenty-two are called autosomes and one pair, number twenty-three, is called the gonosome or the chromosome X. When the pair has two chromosome Xs the sex is female and when it has a chromosome X and a chromosome Y the sex is male. The genes lie in the DNA, which in its turn, is in these chromosomes, as has already been pointed out.

The basic movement of DNA takes place from the nucleus of the cell to its cytoplasm. To do this it passes through the membrane of the nucleus and goes and locates itself in the cytoplasm with the proteins are then ordered. The DNA is reproduced in the nucleus, is transcribed into the nucleus itself, and is converted outside the nucleus, in the cytoplasm, in the ribosome, and, when transformed, it comes to the proteins, which, as has already been pointed out, are located in the cytoplasm itself. It sends its information from the nucleus, this information is transcribed and is transformed in order, in this way, to reach the proteins.

The reception of the information, its transcription and its transformation take place in the ribonucleic acid (RNA), which is called 'messenger' RNA (mRNA), until it goes out of the nucleus of the cell and then becomes 'transport' RNA (tRNA), when it transports the DNA

within the cytoplasm, within the ribosome, so that in this way the amino acids of the proteins can then be ordered. The twenty amino acids of the protein that orders the DNA are the following: arginine, cysteine, asparagine, glutamic acid, phenylalanine, glycid, histidine, isoleucine, lijaid, lysine, methionine, proline, glutamine, serine, threonine, valine, tryptophan, tyrosine, arginine and aspartic acid.

2. The Structure of DNA

The structure of DNA consists of four elements that combine with each other but which in their simplest expression are: a nitrogenous base, two acids and a protein. The nitrogenous base can be 'purine' or 'pyrimidine': the purine is made up of adenine and guanine; the pyrimidine is made up of cytosine and thiamine. The purine and pyrimidine bases are joined through hydrogen connections. The acids are phosphoric acid and deoxyribose (sugar). The protein is histone. The set of these four elements form a nucleotide. The set of nucleotides are chained together and these chains form the DNA.

3. The Structure of RNA

The RNA is different from the DNA in that it has only one band rather than the two possessed by the 'helix' of the DNA. In this band it has the same nitrogenous bases as DNA, with the exception of thiamine which is replaced by another termed 'uracil'. It is thus made up of adenine, cytosine, guanine and uracil. The messenger RNA (mRNA) 'photographs' the DNA in the nucleus and thus transcribes and transmits the information of the DNA to the cytoplasm in order to order the amino acids of the proteins. The information that is 'photographed' by the mRNA is read in the sequences of the three genes that we are referring to and which are termed 'triplets'. These triplets, in their turn, are called 'codons' and act as a mould so that the proteins can be found in them and their synthesis can take place. Together with the codons there is another substance of the RNA and this is called 'anticodon'. The anticodons are entrusted with providing the correct sequence to the amino acids of the proteins, which are shaped in the codons.

Here the RNA becomes tRNA, that is to say transport RNA, and achieves the transfer of families of molecules, each through a different starch of the protein.

The codification of the sequence of the proteins themselves thus takes place and this leads to another element that has its origins in the RNA. This element is called 'exon'. Together with this there is another, the 'intron'. Little is known about the intron. Some say that it helps the exon in the codification. However, when the RNA reaches the ribosome which, as has already been pointed out is located in the cytoplasm of the cell, it eliminates the introns and allows only the exons to work.

4. The Genes

The genes are the units of inheritance ordered in a line in the cell nucleus as a particle of DNA (between 2% and 35 of the acid). Each gene contains many nucleotides. A nucleotide is made up of sugar and five atoms of carbon, phosphoric acid and a nitrogenous base. The nitrogenous base is in its turn made up of four components, namely: adenine, cytosine, guanine and thymine. It is very important to observe that the sequence and the proportion of these elements determines the properties of the gene. The genes act through the molecules of the ribonucleic acid for the metabolism of the organism or for the production of the proteins. The proteins, in their turn, are made up of chains of twenty amino acids. The sequence of the amino acids in a specific protein determines if this protein will form a part of the structure of an organism or of its metabolism.

There are other components of genes in animals and plants that are of a proportion of ten to one in relation to the nitrogen base. But not much is yet known about them.

The internal sequence in the nucleotide is the sequence of the nitrogen bases purine and pyrimidine which in their turn are formed into groups of three that have the name of triplets or 'code genes'. It is very important to note that it is the internal and external sequence of these bases and their proportion that marks the difference between all living beings. An example of a sequence of triplets could be: ATT—-CGC—-CGA—-AAC—-ACG—-AAA.

5. The Genetic Code

The genetic code is the genetic information ciphered by the sequence of nucleotides. The information of the genetic code of the DNA is transcribed into complementary information in the triplets of the messenger RNA, which have the name of codons, and this, lastly, is translated in order to arrange the amino acids of the protein.

Once the whole process has been completed it is now possible to locate the place where the genes are to be found in the human chromosomes. These places receive the Latin term '*loci*'. It is thus possible to determine the work that each gene carries out with each amino acid of the proteins. In this way it has been possible to fill in the map of the human genome, its genetic code.

6. Reproduction

The cells that are thus formed divide and reproduce themselves through 'mitosis' in geometric proportions, each one with its forty-six chromosomes, except in the case of the reproduction of the cells of the gonads which reproduce through another process that is termed 'meiosis', by which the chain of chromosomes which formed a helix of forty-six separates into two halves. One half goes to the ovule and the other to the spermatozoon. When the ovule is fertilised by the spermatozoon it reproduces itself already with the forty-six normal chromosomes through the process of mitosis, thereby forming the blastocyte, the embryo and the foetus.

Conclusion of the biogenetic picture

On the basis of what has been said above, we can reach the following conclusions:

– Life presents itself as a movement.

– As an organic movement.

– As a complementary organic movement that always proceeds on the basis of intricate relationships.

– And it always has a finality.

Life thus emerges as 'a complementary organic movement of relationships and finality'.

II. Life. Movement

If we ask ourselves the following question: what is there beyond biogenetics by which to understand life?, we find the answer in chapter eleven of the Gospel according to St. John, a chapter which refers to the resurrection of Lazarus. Christ says to Lazarus, who has already died, 'Lazarus, come out!' And the passing over from death to life takes place in a visible way with movement: Lazarus who was immobile and covered in bandages began to move, then walked and then came out. Once again the movement that we observed in biogenetics is to be encountered, and now we see it at a shallow level as a local movement: Lazarus comes out; what is there that is connected with life within this movement?

1. The Ancient Definition of Life

I remember an ancient definition of life: life is the ability to move on one's own. The ancients thus told us that life was: *the being or acting of the substance that, according to its own nature or its natural working, is related to movement or to some operation*. One is dealing here with a being that has been constituted in its essential parts and that now launches itself towards life, that is to say towards its internal movement. But what is this movement? Here is the answer: it is what is in capacity and power as such. Life, therefore, is said to be the primordial capacity to be and to act.

2. Organic Movement

In order to clarify this organic movement more precisely, it can be understood better by opposing it to a certain conception of life that is to be located within a mechanistic parameter, where vital movement is seen as a quantic collision.

The organic movement that constitutes life is not a clash of quantity of the Cartesian *res extensa* but a finalistic expansion that transcends quantity, albeit not departing from it. Specifically because of this finality, the vital movement is a movement that we find in the field of relationships and which aims towards a definite finality which specifically ensures that organic life is a unity whereas vital disintegration is death.

3. Organicity

Being acting and acting being. In every movement, however, there are two terms, from one of which one proceeds, and to the other of which one tends. That to which one tends is its finality, which, indeed, specifies and defines the whole of the movement. Whither, therefore, does life tend? I believe that the answer is that life tends towards unity. Organicity is what specifies life, there is a unity that organises the living being from within and there is an unity that organises it from without, that is to say in relation to other beings.

But for there to be organicity there must be a distinction of the parts, a distinction of organs, both within and without – *vice versa* there cannot be unity. Internal unity and the organicity of a living being make it present in life; to generate its organicity is to generate its life. However, this organicity is not limited to within but aims at external organicity, at unity with other living beings. Internal uniqueness confers individuality, however it is not vital if it is not intimately transformed by external uniqueness, by the relationship with other living beings.

External organicity in this way involves individuality, which, indeed, cannot close itself up within itself to be an individual life: it obtains its own richness when it opens to others and achieves the unity, the harmony, and the convergence of the diverse. We could thus say that life is the convergence of distinct beings. External organicity thus becomes, after a certain fashion, internal organicity, without, however, injuring the distinction of living beings.

4. Distinct Beings

Each being can said to be distinct because it has what another being does not have and it does not have what that other being has. There is an aspect of life that implies negation and through this negation life is produced. Such negation implies an affirmation that requires organicity, the same convergence in the unity of different beings – life.

This convergence of distinct beings, which in the final analysis constitutes life in its totality, has been propounded or denied in various ways in the history of thought. One way of doing this is pantheism in all its forms; another is participation. There is also a way of thinking that structures many contemporary currents, namely the basic denial of external organicity, or at least when man has come to embrace the so-called culture or anti-culture of death.

5. The Denial of Distinction: Pantheism

In pantheism distinct organicity does not exist at a real level because barriers have been eliminated: one is everything and everything is one. Thus, pantheism does not explain life because in pantheism there is no real coincidence of distinct beings. Instead, there is an amorphous whole and thus a whole without life. In truth, in pantheism an authentic opposition between privation and possession does not exist because everything is everything.

III. Life as Opposition

In approaches that are distant from pantheism, *vive versa*, an opposition exists, but we should pay attention to the kind of opposition that is envisaged: life is opposition, opposition according to logic can be opposition of contrariety or opposition of contradiction. If we are dealing with contrariety, we find ourselves in the domain of life. If we are dealing with contradiction, it leads us to death. The opposition of contrariety unites what are contrary through a copulative particle – this and this; the opposition of contradiction excludes one of these opposites in order to affirm the other. In excluding one of the opposites there is no longer organicity and thus one cannot speak of life.

In exploring more deeply what has just been observed, we can state

that there is opposition between two contents when the position of one, after a certain fashion, excludes the position of the other. According to what the character of this exclusion is, there are different types of opposition. The opposition of contradiction is irreducible; it takes place between being and non-being; and it does not tolerate a medium term. The opposition of contrariety or contrary opposition ensures that the two contents exclude each other in a special field of being and thus accepts that there is a medium term in the universal field of being. Contrary opposition can be privative or relative according to whether the two contents are opposed by privation-possession or by mere relation.

1. The Opposition of Contradiction in the Concept of Life

There is a mentality in modernity that is strongly based upon the opposition of contradiction. This is the evolutionistic mentality when applied to man, both directly and fully. Indeed, in the evolutionistic mentality the survival of species takes place through a struggle unto death which is an opposition of contradiction, and thus through the survival of the strongest. This is a mechanistic conception which conceives of life a simple contradictory movement of quantic collision.

Probably, many passages of the theory of the evolution of lower beings to man can be explained in some sectors by reference to this struggle for life. But this theory cannot be applied in its totality because even though it is certain that a gradation exists in the contemporary existence of species in the infra-human living world, today a gradualness in these species persists given that the inferior species have not disappeared. And overall they form the organic infra-human sphere.

However, the problem emerges strongly when this explanation of life through contradictory opposition is applied to life itself in the human sphere. In this case, one encounters the opinion that the dominion and the survival of the strongest is a norm and from this opinion spring all the Malthusian views, and views about super-races, according to which some people affirm themselves by trying to kill others, in a savage way in primitive stages and in a sophisticated way in today's world. This is the culture of contradiction or – and this is the same thing – the culture of death or more strictly speaking the anti-culture of death. In this approach, organicity does not exist, life as organicity disappears, and this is because there is no term of contradiction which can be opposed because this has been destroyed. The problem, given that the term of opposition is absolutely indispensable for life, is that life, because this term no longer exists, withers, and one thus comes to the culture of death. There is no term against which to affirm oneself and given that this belongs internally as well to its own organicity, individual life itself perishes. Once again, beginning with the same logic as well, we find ourselves faced with the culture of death.

2. Opposition of Contrariety in the Concept of Life

The authentic opposition that can guarantee life is the opposition of contrariety which, as has already been pointed out in this paper, is expressed through a copulative particle, 'this and that'. In other words, life is organic complementariness, a being lives because that being is opposed to another living being because it does not possess what the other being has but wants to take part in that being's richness. In turn, the other living being lives because, in remaining distinct, it shares in the richness of the first living being. The ideal is for this participation to be without any reduction, that is to say, without taking anything that each one of the living beings possesses in itself. We are faced here by opposition through simple relation.

IV. The Christian Trinitarian Life

1. Life in the Most Holy Trinity

It is this ideal that is realised in the source of the life of the whole of the creation – the Most Holy Trinity. According to what God Himself has revealed to us, the Most Holy Trinity is made up of a relative opposition and an absolute coincidence. This is what is meant when we say that God is one in three distinct persons. In God, the opposition between the divine persons is an opposition of relation, without privation involving reduction and without possession meaning any diminution of the other person. The opposition between the divine persons is an opposition of relative contrariety. This means that what one person has is related to what the other person possesses so that privation remains in an infinite possession. This apparent contradiction is clarified when we consider the three divine persons in concrete terms: the Father does not have filiation, however He is Father through filiation; the Son does not have fatherhood, however he is the Son through fatherhood; and the Spirit does not have active inspiration, however he is the Spirit through the active inspiration of the Father and the Son. The infinite life of the three divine persons is realised through an absolute and total

giving of that life, from the Father to the Son, from the Son to the Father, from the Father and the Son to the Spirit, and from the Spirit to the Father and the Son. For this reason they are one God. The distinction of the three divine persons is only through an opposition of relative contrariety and with their opposition of relative contrariety they are life in itself, that is to say one God and three distinct persons at the same time.

From this divine model we can grasp that life is a moving on its own in a set of relationships towards full giving. One gives what one has and one receives what one does not have in an unending process that enriches and which is, precisely, the vital process. The fundamental points are the relationships which form the basis of the contrary opposition, not to close up within one's own possession or in one's own privation but to open oneself up in a to-

tal giving. Thus life is a fertile relationship of loving giving.

This is life in itself and when God transmits it to His creation, and in a special way when He transmits it to man, He does so in this way. Gods writes this giving into human freedom. When man does not want to move to this giving, he closes himself up within himself, he opposes himself to other in contradiction. This is sin and also death, which is the same thing.

2. The History of Salvation

The history of salvation is written into the domain of these co-ordinates as a history of freedom. And just as man chose the opposition of contradiction, sin and death, and God, despite this, did not remove from what from within him continues to be His image, so the history of mankind came to be a history that is realised in two terms: contradiction-contrariety; death-life; hatred-love; selfishness-giving.

3. The Paschal Incarnation

In this domain the paschal Incarnation came to carry out the breaking of contradiction in a loving construction of relational contrariety. That is to say, death came to be defeated by the resurrection. Christ took upon himself the contradiction of man represented by his sin and his death, and he took it upon himself to the point of suffering it in himself with the suffering of death. But this death, through the love of the Holy Spirit, was transformed into a source of life, into resurrection. Death was located as the highest test of love, the highest test of giving. And thus Christ, who was not blameworthy for the absolute contradiction of man, recreated the new man in a relationship of justice and holiness. This is the illogical profundity of history that only the Omnipotence of God-Love can make logical, as the highest human expression of the Truth – Christ, the Word of God made Flesh.

4. Contradiction Taken on in Contrariety

Following the central argument of this analysis, Christ took upon himself contradiction and transformed it into a relational contrariety of the greatest love and thus of the greatest life, contrariety in which he opposed himself relatively to man as a subject to whom he gave what was lacking to him in totality – life. The Trinitarian life of contrary opposition of pure giving now passed through the contradiction of death in order to defeat death itself and to transform it into pure giving in the Spirit. He converted it into giving of pure love. The contradiction of death was overcome in the relative opposition of contrariety which is a relationship of love. It has already been observed that the opposition of contradiction generates the culture of death. In Christ, this opposition led him to the greatest death, so to speak, and thus the Redemption involved the transformation of this greatest death into the greatest life, transforming contradiction, through the Spirit, in a pure relationship of love, as total giving. This is the ultimate meaning of the resurrection.

If, as has been argued, life is the ability to be and to act, we can now conclude that life is the capacity to be and to act through a contradictory opposition, namely death, contrary opposition as a relationship of absolute loving giving in which one receives the participated life of the Most Holy Trinity. Life is thus the Resurrection.

Conclusion

In this analysis that I have engaged in on certain elements of bio-genetics that describe the beginning of human life, an initial conclusion was outlined that expressed the view that life is 'a complementary organic movement of relationships and finality'. When the analysis proceeded further into the philosophical aspect what had been previously affirmed was confirmed, in the light of the resurrection of Lazarus as well, and it was observed that life is 'moving on its own', and that this implies a vital opposition that to be such must not be of contradiction but of contrariety, that is to say of integration. From a theological point of view it was seen that life can be nothing else but an opposition of contrariety, that is to say of integration, but one which passes through the contradiction of death, in the history of salvation.

To conclude, we can say that life is love. Only love breaks the contradiction of death and transforms its absurdity of total destruction into an inexhaustible source of life. What is illogical is converted into full and total rationality. It was the historical logic of Love that impetuously irrupted into the world in the Mystery of the paschal Incarnation. Thus should we understand Tertullian's aphorism: '*Credo quia ineptum*'. Thus life, sustained by full trust in He who made it triumph in the resurrection of Jesus Christ, which is the giving of love, flows forward victoriously and illuminates the darkness of death.

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ANGELO SERRA

Introduction to the First Day

I would like to engage in a very brief introduction to this first day of the proceedings on a subject that is today of passionate interest and also of extraordinary importance for the future of medicine.

My *first thought* is to thank His Eminence Cardinal Javier Lozano Barragán, the President of the Pontifical Council for Health Pastoral Care, who wanted with this international conference to present those who are involved in treating and looking after sick people with a very recent step, made up of science and technology, that is opening up really new paths for a great development in medicine.

I take my *second reflection* from the editorial at the front of the very extensive issue of the well-known journal *Science* of 16 February 2001 which contained the results of the sequencing of the human genome that had been achieved over eighteen years of intense work by hundreds of laboratories throughout the world, results coordinated by the Human Genome Project. That editorial reads as follows: 'Mankind has received a great gift. With the completion of the sequencing of the human genome we have received a powerful instrument by which to uncover the secrets of our genetic inheritance and to find our place amongst those others who take part in the adventure of life'. *The text of the secret code of the plan-programme of our biological lives*, indeed, had been translated, a text written in a molecular language in twenty-three chapters – the twenty-three chromosomes. Over the next four years this text was then *written down*, with the discovery and attribution of specific information, namely *genes*, of which today, that is to say by 23 October 2005, 20,065 are known about at the level of their structure and their function. Another 35,329 so-called 'putative' genes are still being studied.

These have been extraordinarily rapid steps and they have opened up a path made up of great advances and expectations but also a path made up of dangerous projects and risks if science, technology and society allow themselves to be overwhelmed by the attractive but blinding Promethean temptation of omnipotence.

My *third thought* is a keenly-felt and sincere expression of gratitude to all those who agreed to offer their profound skill and expertise in these advanced fields of science and knowledge in the space of a few minutes. I am certain that from the proceedings of these days there will emerge a mosaic where every piece of that mosaic will make the greatness of so many advances achieved by science shine forth, and where every caption in Gothic characters – the outcome of the second day of the proceedings – will express the thought of wisdom illuminated by a light that is not only human.

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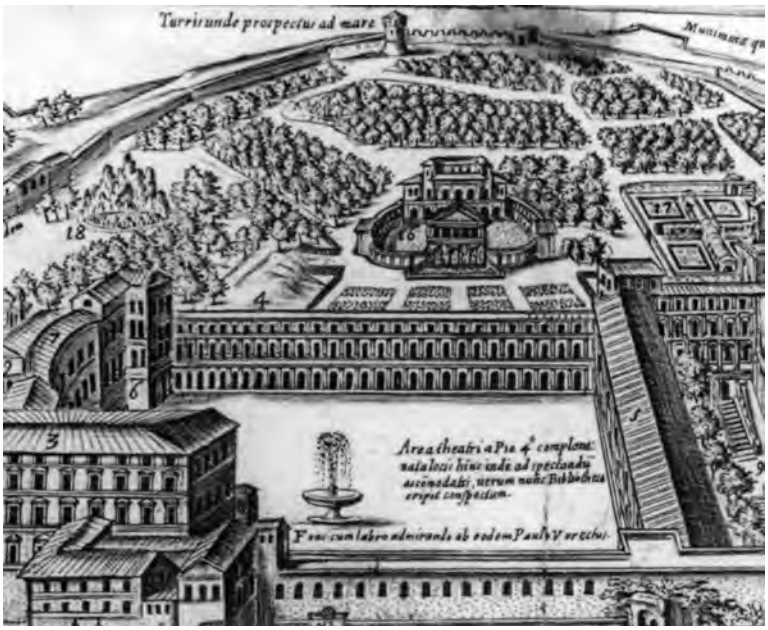

First Session

The Contemporary Situation

GEORGE ROBERT FRASER

1. Human Genetics Today: Hopes and Risks

It is in this very same city of Rome that I gave my first talk at an international congress, 44 years ago in 1961, on *The Pool of Harmful Genes in Human Populations* (Fraser 1962a), a topic subsumed within that of the present subject, *Human Genetics Today: Hopes and Risks,* a vast panorama which retraces the entire history of the development of our human species as documented in the common heritage of our human genome in all its diverse, and yet harmonious, complexity. In this short talk, in conformity with the written presentation of the aims of this conference, I shall confine myself mainly to the perspective of health, leaving aside many other aspects of human genetics; this leads to the corollary that the term human genetics will be largely interchangeable with that of genetic (or genomic) medicine. And I shall speak of the hopes and of the risks attendant on the process of integrating genetic medicine into the science and the art of medicine and medical practice as a whole, a process which is being pursued intensively at the present time.

As part of this perspective of the application of human genetics to health, the recent description of the sequence and topography of the human genome (the Human Genome Project) represents an important advance which has led to the accumulation of a vast and rapidly increasing body of knowledge about our hereditary material. A vast body of knowledge, however, is insufficient in itself to make a major impact on health; the wisdom to make use of the knowledge is also indispensable. In the acquisition of this wisdom, humility rather than arrogance must be our guiding principle Thus, the pre-Socratic philosopher, Xenophanes of Colophon, wrote, among the few fragments which have come down to us of his thoughts about the limitations of human knowledge:

The gods did not reveal all things to mortals in the beginning;
but in long searching man finds that which is better.
ΟΥΤΟΙ ΑΠ'ΑΡΧΗΣ ΠΑΝΤΑ ΘΕΟΙ ΘΝΗΤΟΙΣ'ΥΠΕΔΕΙΞΑΝ, ΑΛΛΑ ΧΡΟΝΩ ΖΗΤΟΥΝΤΕΣ ΕΦΕΥΡΙΣΚΟΥΣΙΝ ΑΜΕΙΝΟΝ.

When we consider our human genetics of today, while we may justifiably claim that we have made progress along the road towards that which is better, we should not delude ourselves into believing that in our searching we have taken more than the first few steps along this road; nor should we flatter ourselves that these few steps have all been taken in the modern era. For example, among the ancient Greeks from the sixth century BC onwards, Anaximander, Hippocrates, Aristotle and Plato, among others, wrote about the mechanisms of inheritance; as well as about those of evolution. To introduce a very striking example which says much about one of the major risks of human genetics today in the context of unjustified and unjustifiable attributions to individuals of hereditary superiority and inferiority, Plato applied such ideas extensively 2500 years ago to what we would now call eugenic principles, especially in the fifth book of the Republic, a chronicle of the regulations which would govern the functioning of the hypothetical city where justice would reign supreme. In this quotation, Plato passes from considering the practices involved in the breeding of hunting dogs in order to maximise their skills, to the mating patterns which should be applied to the Rulers or Guardians of the city.

It is necessary, given our agreed premises, that the best men should mate with the best women in as many cases as possible, while the reverse should hold for the worst men and women; and we should rear the offspring of the former, but not of the latter, if our flock is to be of the highest quality.

To move fast forward 2 1/2 millennia to the 19th century, in the words of Theodosius Dobzhansky: *Genetics, an important branch of biological science, has grown out of the humble peas planted by Mendel in a monastery garden.* The achievements of Abbot Gregor Johann Mendel can without any hint of hyperbole be described as unique in the annals of science and we have built on these achievements over the past 140 years to accumulate the vast body of knowledge of which I have spoken.

Until very recent times, the role of the human geneticist in medicine has been largely confined to giving

advice and counselling about the role of heredity in the causation of disease and handicap among those who consult him, and their offspring, especially with respect to the evaluation of rare monogenic Mendelian disorders, birth defect syndromes and chromosomal anomalies. His role has definitely not been in following the eugenic precepts of Plato in encouraging reproduction in one group of the population and discouraging reproduction among others. One advantage which has accrued to us with the accumulation of knowledge is that we now know that, in addition to the lack of any moral basis for such selection of the parents of the next generation which was being practised until recently, there can also be no rational basis for any such selection from among the virtually infinite variety of our genetical endowment.

Thus, in 1966, my late mentor, teacher, and friend, Professor Lionel Penrose wrote: *The social and biological values of hereditary differences are continually altering as the environment changes. We cannot be sure that any gene will be bad in all circumstances and much less sure that any gene is always good. At the moment we are only scratching the surface of this great science and our knowledge of human genes and their action is still so slight that it is presumptuous and foolish to lay down positive principles for human breeding. Rather each person can marvel at the prodigious diversity of the hereditary characters of Man and respect those who differ from him genetically. We all take part in the same gigantic experiment in natural selection.* (Penrose 1966).

Human genetics today is in no sense to be regarded as a surrogate for the discredited eugenic ideas of the past; it is rather to be regarded as an integral part of medicine with the role of incorporating the knowledge which is being gained about the human genome into diagnostic, preventive and therapeutic activities, whether directed towards the foetus, the infant, the child, the adolescent or the adult, within the context of the family unit, there being no discontinuity between these phases of human existence. In this context, the practice of selective abortion of foetuses diagnosed *in utero* as being affected by a genetically determined disease or malformation is contrary to the tenets of our medical tradition with its emphasis on the preservation of life, and this may best be regarded as a transient phase in the development of genetic medicine, which will be superseded in time by methods which will be more generally acceptable.

Pre-implantation diagnosis has been put forward as an alternative, and is being practised in some centres, but this has given rise to ethical controversies connected with the moral status of the embryo. Turning from selection at the level of the foetus and of the embryo to selection at the level of the gamete, reliable separation of the husband's sperm into X- and Y-chromosome-bearing fractions, followed by fertilisation of the wife using only the X-chromosome-bearing sperm in order to avoid the births of males when the wife is a carrier of an X-linked disorder such as Duchenne muscular dystrophy, may become possible in the near future and may be less open to objection on ethical grounds. It would be foolhardy, however, to forecast the attitudes and practices of future generations with respect to these problems in general, especially since they will have access to technologies whose nature we cannot now foresee.

There are experts assembled here who will be telling you over the next three days in detail about each and every aspect of this integration of human genetics into the practice of medicine. Of course, the present important role of the medical geneticist as a non-directive counsellor will always continue to be needed, and will expand in parallel with the expansion of knowledge about the role of heredity in the aetiology and pathogenesis of disease. A remarkable example of such expansion has been the relatively recent creation of a very large subspecialty of genetical counselling in the field of cancer, as a result of the discovery of gene loci harbouring alleles at a substantial frequency, which give rise to a strong predisposition to various forms of this common disease, often at a tragically young age.

In fact, it has always been evident that heredity plays a role in the aetiology and pathogenesis of virtually every disease state, but we have not been able previously to define the mechanisms of this involvement. We are now in a position to begin this task, and, as a result, to start thinking about therapeutic modalities of correcting inherited defects, diseases and disabilities. There is a perception that genetic profiling is going to be the cornerstone of this endeavour in determining the genetic complement of individuals at large numbers of chromosomal loci, and thus defining their specific susceptibilities to common diseases, indicating possibilities of prevention and treatment, and also, in the same manner, predicting the variations to be expected in the efficacy or toxicity of therapeutic agents, providing pointers to tailoring therapy to the patient (pharmacogenomics). This genetic profiling will supplement the many types of genetic testing and screening for individual genes, which is currently being performed and which will continue into the future.

Apart from the prospects opened up for advances in health care by such genome-wide extensions of determining the genetic complement of the individual, genetic medicine has been enriched by a new armamentarium of methods involving gene therapy – the treatment of genetic disorders by introducing specific engineered genes into the cells of the patient, which began in 1989 with the successful treatment of a rare recessive im-

mune disorder, adenosine deaminase (ADA) deficiency, also known as severe combined immunodeficiency (SCID) syndrome. The possibilities of such gene therapy in replacing the function of defective genes will increase with the increased use of cultured and modified pluripotent stem cells which have retained plasticity in that they can be integrated into multiple tissues. It may become possible to derive such pluripotent cells from adult tissues in the future, thus obviating the ethical problems of using embryonic stem cells.

I should emphasise that this brief summary of possible applications of advances in our knowledge of the human genome to the treatment of disease represents hopes, or prospects, for the future, rather than present-day realities. We are, in fact, at the starting point of the long searching for that which is better which I mentioned at the beginning of this talk in connection with the sentiment of Xenophanes. We can just begin now to entertain hopes for improvements in the treatment of common diseases of adult life such as diabetes mellitus of adult onset (type 2), cancer, atherosclerosis, hypertension and others. Such diseases have multifactorial causation mediated by complex interactions of environmental factors with multiple genes determining susceptibility, which are now being intensively investigated by the establishment of the haplotype map, or HapMap, of the small proportion of gene loci where the DNA sequence varies between individuals (SNPs or single nucleotide polymorphisms). It should be noted that many agents which have been implicated as environmental triggers of such diseases in genetically susceptible individuals, are so deeply ingrained in our way of life that they are hard to avoid. These contributory factors include smoking, unbalanced or excessive diets, a sedentary existence, and exposure to stress, primarily among inhabitants of wealthy nations where excess rather than scarcity is the hallmark of society, and where life expectancy has increased so that the large majority of the population survive into adulthood. Unfortunately, the abolition of the use of tobacco and its products, and the adoption of a healthy diet, are projects which, while very simple in their conception, are difficult in the extreme in their execution. In this context, fields of genetic medicine are being developed today specifically in the area of studying the effects on the individual of pollutants and toxins such as tobacco (toxogenomics or toxicogenomics) and of diet (nutrigenomics).

In the case of cancer, a group of diseases in which mutations in somatic rather than germ cells usually play a primary role, pharmacogenomics can already contribute to the better care of some types. For example, if testing reveals that the genetic complement of a newly diagnosed breast cancer results in the presence of human epidermal growth receptor 2 (HER-2) on the surface of the cell, as is the case in 25-30 per cent of all such patients, then adding the drug herceptin or trastuzamab to the therapeutic regime, is thought to lead to a remarkable improvement in prognosis. Much is also expected of gene therapy for the improvement of prognosis in various other forms of malignant disease. Improved knowledge of the genetic mechanisms involved in pathogenesis can also contribute to earlier detection of cancers when the malignant cell mass is much smaller and the prospects of successful treatment much more promising.

It should be noted that the approaches to therapy by defining aberrations of cell function as a preliminary to correction, which have been discussed, must be accompanied by major advances in computational biology. It is not sufficient to have a catalogue or data base of the gene complement of an individual. At least an elementary understanding is needed of the patterns of the virtually infinite number of first, second and higher order interactions between the myriads of genes (genomics), mRNA gene transcripts (transcriptomics), proteins (proteomics), glycans (glycomics) and metabolites (metabolomics), which underlie the phenotype and physiology of a single cell. And the functioning, healthy or diseased, of a body organ cannot be defined merely by making an inventory of the functioning of its constituent single cells.

Because of the complexity of multifactorial causation depending on the complex interaction of environmental factors with multiple genes determining susceptibility, the development of prevention and treatment for common diseases, including those which have been mentioned, will always be very difficult. But these difficulties will have their compensations. For example, in the case of cancer, the discovery of gene loci (BRCA1 and BRCA2 responsible for breast and ovarian cancer, and others), harbouring, at a substantial frequency, alleles which give rise to a strong predisposition to various forms of this common disease, often at a tragically young age, has already been mentioned. All common diseases are heterogeneous in their aetiology and pathogenesis, and there are unusual rare forms subsumed within the generality of each common disease, which are inherited in a simple monogenic manner as in the case already cited

of breast and ovarian cancer due to mutations at the BRCA1 and BRCA2 gene loci. Intensive study of these monogenically determined subgroups of cancer, diabetes mellitus of adult onset (type 2), atherosclerosis, hypertension and other common diseases, and the uncovering of the genetical abnormalities involved in rare and unusual families of this type, will throw light on the aetiology and pathogenesis of these diseases in general, in part by suggesting leads to the discovery of genes involved in susceptibility to the more common forms.

During these voyages of discovery, as in so many others, we shall be following the precepts contained in a prescient and much-quoted extract of great beauty and power from a letter written by William Harvey in 1657, six weeks before his death, to John Vlackveld, a physician of Harlem in the Netherlands, in reply to an enquiry about a patient. Harvey wrote his letter in Latin, the lingua franca in use within the medical profession at that time.

Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of rarer forms of disease. For it has been found in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way. (Translation from the original Latin into English by R Willis (1847))

Non solet natura usquiam penitiora sua arcana apertius detegere, quam sicubi extra consuetam semitam tenuia sui vestigia monstraverit: nec est ad medicinam recte faciendam tutius iter, quam si quis ex morborum raro contingentium diligenti scrutamine, ad usitatam naturae legem dignoscendam, animum transtulerit. Quippe ita fere in rebus omnibus comparatum est, ut quid illis insit commodi, cuive usui potissimum inserviant, nisi earundem carentia, aut vitiosa constitutione aliqua, vix satis perspicamus. William Harvey (1657)

Thus, careful investigation of these rare monogenically determined forms of heterogeneous common diseases cannot fail to throw a great deal of light on the mechanisms of pathogenesis of the corresponding common disease in general.

To turn now to rare genetically determined malformation syndromes, to which, of course, this perspicacious precept of Harvey applies *a fortiori*, the name of my late colleague and friend, Professor Jérôme Lejeune, is well known at this conference in this context, and I should like to say a word about the disease with which his career was mainly associated, the Down syndrome due to a chromosomal aberration resulting in a trisomy of chromosome 21 which he himself discovered in 1959.

In 1981, Professor Lejeune wrote: *Que savons-nous de la trisomie 21, après vingt ans de recherche? Quel sujet de méditation et d'inquiétude aussi! Certes, nous avons appris bien des choses, et même à reconnaître la maladie chez des enfants très jeunes, encore au ventre de leur mère. Mais si ce pouvoir nouveau a suscité chez certains la tentation d'éliminer les malades extrêmement jeunes, cette connaissance n'a fait en aucun cas régresser la maladie.*

Et c'est pourtant la maladie qu'il faut vaincre, et les patients qu'il faut guérir! (Lejeune 1981).

What do we know of trisomy 21, after twenty years of research? What a topic this is for meditation and also for deep concern! It is true that we have learned many things, even to the point of recognising the disease in very young children, still carried within the body of their mother. But if this newly acquired power has given rise in some to the temptation to eliminate these extremely young patients, this knowledge has not given rise in a single case to any regression of the disease.

And yet it is the disease which must be vanquished and the patients who must be cured!

Professor Lejeune always remained convinced that these patients could be treated and cured. He thought of the manifestations of Down syndrome as symptoms of a disease to be vanquished, and he totally disagreed with many of his medical colleagues who thought of the condition, following antenatal diagnosis, as a symptom of death, thereby perverting the traditional goal of medicine from a cure to an assault on the patient. He said that he looked forward to the day when a patient with the Down syndrome, treated successfully, becomes a successful geneticist. Possibly, in the new era of functional genomics, some way will be discovered of inactivating the supernumerary copy of chromosome 21, perhaps by learning from the mechanism of inactivation of one of the X chromosomes in females.

The question and statement by Professor Lejeune quoted above, echoes another reflection written by William Harvey, extracted from the dedication of his remarkable book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (1628), in which he describes his discovery of the circulation of the blood. The intellectual humility manifested in this extract, despite its exalted provenance from a classic text occupying a fundamental position in the annals of scientific progress, is as relevant today as it was when it was written in the 17th century. It serves as a reminder, if one were needed, of the vast extent of our present ignorance, and as a cautionary antidote to any misplaced conceit with respect to the limited extent of our present knowledge in the field of human genetics, as in other fields of scientific endeavour.

Nor are they so narrow-minded as to believe that any art or any science was ever so absolutely or perfectly taught in all points by the Ancients, that there is nothing remaining to the industry and diligence of others, for there are indeed a great many who openly confess that the greatest part of those things which we do know, is the least of the things which we know not. (Translation from the original Latin into English by G Witteridge (1976))

Nec tam angusti animi ut credant quamuis artem aut scientiam adeo omnibus numeris absolutam et perfectam a veteribus traditam, ut aliorum industriae, et diligentiae nihil sit reliquum: cum profiteantur plurimi, maximam partem eorum quae scimus, eorum quae ignora-

mus minimam esse. William Harvey (1628)

I should like briefly to mention one more rare genetically determined malformation syndrome, the autosomal recessive multiple malformation syndrome of cryptophthalmos to which my name has been attached as an eponym on the basis of a paper which I wrote more than four decades ago (Fraser 1962b). Over the past three years, two gene loci have been identified where mutant alleles responsible for this heterogeneous entity reside, and the mutant alleles themselves and the proteins to which they give rise have been characterised. Thus, the cryptophthalmos syndrome has entered the modern age of genomics with its hopes for eventual prevention and treatment.

The disabilities associated with the fully expressed form of this condition are even more serious than those associated with the Down syndrome, and yet there are families who are bringing up such children in an atmosphere of harmony and happiness. In a recent case in Germany, antenatal diagnosis of a fully affected female was followed by major foetal surgery on her malformations to ensure her survival, rather than by abortion—not gene therapy *in utero* as yet, but at least conventional treatment in foetal life of a fatal Mendelian disease.

One of the girls in my 1962 paper was eight years old at that time. I had first met her at the age of six years when she was deaf and blind; she was behaving like a wild animal, reacting with frightened screaming to any attempted approach. I noticed that she liked to press loudly ticking clocks to her skull and, suspecting that her deafness was largely conductive, I took her to an otorhinolaryngologist of my acquaintance. He reconstructed her malformed outer and middle ears, and, at the age of seven years, she heard speech for the first time; 45 years later, she lives a life which has been more tolerable than it would have been without any hearing. Perhaps this small contribution to the improvement in the quality of the life of this girl represents a greater achievement than that of my name becoming attached to a syndrome, and even, in abbreviated form as FRAS1, to a gene and to a protein.

There is no doubt that the bringing up of such a disabled child can be an enriching experience for the family if society is prepared to provide some relief from the economic burden involved. Moreover, society as a whole can benefit from such an investment in terms of rewarding employment and spiritual enlightenment, as a result of co-operation in the support and education of such children.

As long ago as the 16th century, in his essay, Of a Monstrous Child, Michel Eyquem de Montaigne (1533-1592) wrote: *"Those whom we call monsters are not so with God, who in the immensity of his work sees the infinity of the forms therein contained."* Four hundred years later, Professor Lionel Penrose who shared with Professor Lejeune his love for patients with the Down syndrome, wrote in 1971, the year before he died—*The object of medical science in civilized communities is to keep people alive. This principle has no exceptions and it applies also to low-grade defectives of all kinds... Not only are these low-grade defectives harmless, they are not responsible for their own condition; they can be happy and they can stimulate human feelings and parental love. By all canons of civilized society, they have a right to demand care and comfort even if they are unable to give adequate returns. The ability of a community to make satisfactory provision for its defectives is an index of its own health and progressive development; the desire for their euthanasia is a sign of involution and decay of human standards.* (Penrose 1972)

I should like now to return to the quotation from Plato with which I began this lecture, containing ideas associated with positive eugenics, or improvement of human qualities, to be realised by controlled assortative matings between individuals with superior qualities, however their superiority is defined. The application of human genetics to medicine should be thought of in terms of the individual and of the family, as in the case of all other branches of therapeutic medicine, and not in the context of future generations. It should also be thought of primarily in terms of combating disease and not in the context of enhancement of the potential of the child. Genetic engineering directed towards the transfer of genes determining higher levels of intelligence or of musical ability, or modifying behaviour in socially desirable directions may never be realised; it is not even going to be possible to find universally acceptable definitions of the quality of the 'enhancement' which could be obtained by such methods if and when such genes are individually identified. We have neither the knowledge nor the wisdom to pursue the eugenic illusions of the past with respect to any hypothetical improvement of our species, and Plato's analogy drawn from breeding hunting dogs is as inappropriate and as irrelevant as analogies drawn from present-day cattle-breeding in order to maximise milk production. While human beings are not candidates for genetical engineering of 'improvements' by such means, they are able to benefit greatly from improvements in education, both qualitative and quantitative in the sense of extending opportunities for the best education to wider segments of society.

With respect to the goal of negative eugenics, also reflected in Plato's writings, of reducing or eliminating the reproduction of the inferior and unfit, not only do we lack the knowledge and wisdom to define the inferior and unfit, but, in addition, all human beings who do not suffer from a condition which renders them infertile have the right to procreate. This right is enshrined in the United Nations Universal Declaration of Human Rights *(Article 16-1—Men and women of full age, without any limitation due to race, nationality or religion have the right to marry and have a family.).* No human being has the power to interdict the exercise of this right by another human being. And if genetic medicine allows reproductive transmission of hereditary traits which precluded reproduction before treatment became available, any increase in the population frequency of the genes determining such traits will represent a totally insignificant modification of the gene pool.

The primary task of our society is to ensure, entirely independently

of the introduction of genetic medicine, the careful conservation of the environment, and hence the transmission of an intact and undiminished physical heritage to our descendants. This is a *sine qua non* with respect to the preservation of our civilization and of our planet from major catastrophes resulting from our newly acquired mastery of the technological means of self-destruction. Provided that this will be so, these descendants will then be able to ensure the careful conservation of an intact gene pool and the continuing transmission of an undiminished biological heritage, using means whose nature we cannot predict, or even imagine, since they will be based on discoveries which are yet to be made. In the words of Francis Bacon (1561-1626)—*Men must pursue things which are just in present, and leave the future to the Divine Providence.*

What then are the hopes and the risks of this modern transition of human genetics to illuminate and inform a much broader spectrum of medical activity—human genetic medicine? The main hope is a simple one and it will undoubtedly be realised—an improvement in the health of the population. But the realisation of this improvement will carry within itself its own risk—the accentuation of inequality and injustice. Thus, these new medical activities are both very expensive, and very difficult to implement, and their benefits will not be equally available to all members of the human family.

Unfortunately, moreover, the main current sources of morbidity and mortality in the materially disadvantaged, or, in many cases, dispossessed, majority of the population of our planet, are derived from scourges such as, for example, famine, lack of access to clean water and infectious diseases, where the predominant role of the environment in the determination of the associated adverse effects overwhelms the role of genetical variation. In striving to mitigate the effects of such scourges, we must also ensure that the potential benefits of genetic medicine will not be confined to a few individual members of prosperous societies. Inequalities in access to the benefits of genetic medicine are particularly anomalous precisely because the human genome which is the topic of this conference, is the joint heritage of the world-wide family represented by the members of our species, and constitutes both the pledge and the indelible hallmark of its intrinsic and immanent unity.

Indeed, progress in the direction of equity in access to health care in general is not an optional matter; rather, it is an essential requirement for the long-term stability of our society. Thus, for example, in 1999, women in Japan had a life expectancy of 84.3 years while in Sierra Leone women had a life expectancy of 42 per cent of this figure at 35.4 years. Pope John Paul II wrote in the Evangelium Vitae in 1995—*Life is always a good. This is an instinctive perception and a fact of experience, and man is called to grasp the profound reason why this is so.* Such an inequitable distribution of this good is a disgrace to our civilization as well as a major source of social and political unrest.

To return to our hopes for genetic medicine, I shall not be mentioning possible applications and uses in the fields of reproductive cloning, germ-line gene therapy, and postponement of ageing; these topics lie outside the main stream of this short talk. In passing, it would seem presumptuous to embark on major projects involving germ-line gene therapy with its potential effects on future generations, at a time when somatic cell gene therapy has only reached an early experimental stage.

As I have already indicated, some of the major avenues which will lead to therapeutic advances will be in the field of pharmacogenomics, a science which will lead to the development of small-molecule drugs to modulate disease-related pathways in the desired direction and will refine our knowledge of the variation in the reaction to drugs already in use, helping to avoid the occurrence of side effects which can often be serious. The genetic basis of such reactions to the large range of antipsychotic drugs which are being so widely prescribed in our society, would seem to be a potentially fruitful field for study. I have also mentioned gene therapy as a therapeutic modality which already shows promise in the treatment of diseases such as severe combined immunodeficiency (SCID) syndrome by replacing the function of a defective gene by adding a normal one, even though progress is slow and attended by setbacks representing undesirable results of the procedures used to introduce the normal gene. An alternative strategy which shows promise of avoiding detrimental effects is to replace only the mutated sequences of the abnormal gene, to repair its function rather than to replace it.

Predictive genetic tests for predisposition for common disease will become available, allowing tailoring of protective measures involving changes in life styles and drug administration, to individual genetical susceptibilities. In this field, particularly great care will have to be taken to avoid discrimination with respect to employment and insurance. The mantra of genetic medicine is that genetic pro-

filing will permit the tailoring of health care, preventive strategies, treatments and interventions to the individual, and will therefore make personalised medicine possible. There are major ethical. legal and social implications of this genetic profiling information particularly in areas such as privacy, insurance, employment, and education. All these implications are connected with risks, and within the Human Genome Project, 3-5 per cent of all funding has been devoted to the study of such ethical, legal, and social issues (ELSI). In addition, I have already mentioned that the expense of genetic medicine can be considered as a risk involving discrimination on economic grounds in that inequitable distribution of health benefits will heighten the already considerable tensions besetting our society.

There is a risk, moreover, that the vast accretion of knowledge about their own genetic complement and the potential harmfulness of some of its constituents may be psychologically deleterious for many individuals and cause them severe anxiety rather than influence them to adapt their life style to their genetic constitution. The remedy is to increase the awareness and expertise in these respects of members of the health care profession so that they can play an enhanced educational role.

We must also consider the risks attendant on the commercialisation of every aspect of human genetics and genetic medicine. This involves the introduction of unjustified testing on a large scale, the patenting of DNA sequences so that royalties become payable on laboratory procedures, greatly increasing their cost, the reluctance to develop drugs for the treatment of rare 'orphan' diseases, and the development and patenting of drugs on the basis of false premises. For example, the Federal Drug Administration (FDA) in the USA has very recently approved a drug called BiDil to treat heart failure in self-identified African Americans and only in self-identified African Americans on the basis of a trial (A-HeFT or African American Heart Failure Trial) which only enrolled such individuals. This episode certainly does not represent an advance in pharmacogenomics or in personalised medicine, and, in fact, has some very grave implications from the point of view of racial discrimination which have been discussed by Kahn (2005).

Thus, while the distribution of genes at the very small proportion of loci where variation occurs, may be different in different races, race in itself is not a genetic trait. In this connection, in 1966, Professor Penrose wrote: *The exact description of the hereditary polymorphisms in our species, which overrun the boundaries of antiquated ideas of racial groups. helps us to comprehend, rather than to deplore, each other's inborn peculiarities.* (Penrose 1966). Nevertheless, discrimination on the basis of supposed and even real differences in the frequency of various genes between different ethnic groups represents a substantial risk arising from the development of human genetics. There are various very large research projects collecting blood and other samples to provide genetic information about gene distributions in large groups of individuals. There is the Human Genome Diversity Project of HUGO (Human Genome Organization) and there are many Biobanks of various sorts containing large quantities of blood and other samples. While such projects have value in studying such topics as human evolution and migration, as well as differential susceptibility to disease, they also present major risks of misuse and abuse in the realms of political, social, educational, medical and economic discrimination. Privacy and confidentiality must be primary considerations affecting storage of the data. Such risks of misuse and abuse are much intensified when attempts are made to identify genes responsible for intelligence and for normal and abnormal, including criminal, behaviour, with a view to studying their differential ethnic distribution. So far, no genes have been identified, which have a direct effect on non-pathological variation in intelligence and behaviour, not associated with disease; it may never be possible to do so.

As I have indicated, the hopes attendant on human genetics today can be summarised as the promise of better health in the long term, inseparably connected with the promise of a greater respect for human life in association with the increasing realization that all the members of our species are inextricably bound together by the possession of the common heritage of our human genome. These hopes can only be achieved against a background of improved education of the public and especially of the healthcare profession, and of a concerted attack on the global inequality which shames our civilization.

Many of the risks of human genetics today involve geographical, ethnic, and class discrimination leading to restrictions in the beneficial use of the information which is being so rapidly accumulated. There is also the risk that we shall not only fail to use this new information for the benefit of all members of our human species, but actually misuse it to obscure and justify existing inequalities, thereby entrenching the privileges of a small self-selected minority of members of our society who consider themselves to be superior, to the extent of denying the right to reproduction and of life itself to the majority of the weak and vulnerable, whether the weakness and vulnerability are based on poverty or ill-health, or on unjustifiable attributions of lack of fitness on the grounds of physical or intellectual inferiority. A comment by Professor Penrose is relevant in this context—*New discoveries may take everyone by surprise and scientists have to be continually on guard against misuse of their discoveries by those whose knowledge is incomplete* (Penrose 1966).

We have in part uncovered the nature of the human genome; within the boundaries of this unitary human genome, we cannot define individual overall genetic complements which are qualitatively superior or inferior. Unfortunately, however, such misguided notions of superiority and inferiority, based as they are on incomplete knowledge, are deeply entrenched in our collective psyche and are expressed explicitly even by such revered thinkers as Plato. The disastrous corollaries of these notions in the form of exclusion and of murder have been put into practice repeat-

edly, culminating in the vast scale of the exclusions and murders which have blighted many regions of the world during the troubled century just past. As we face the dangers of the century to come, we must find the wisdom to prevent the great scientific achievements which have led to the human genetics of today, and which can be regarded as the antithesis of these reverses to which our society has been subject during this period, being used to support such divisive practices, thereby increasing the risk that social and political discord and dissension will jeopardise the future of our civilization.

In general, we must guard the integrity of our human genome, the joint heritage of the world-wide family represented by the members of our species, entirely independently of class and of ethnic origin, by putting an end to our ecological depredations and by applying ourselves sedulously and meticulously to the protection of the environment from further damage, thereby ensuring the transmission of an intact and undiminished physical heritage to all our descendants so that they are enabled to foster their biological heritage in an appropriate manner in order to underpin improvements in their physical and social circumstances. In this context, I conclude by quoting the last two sentences of the talk which I gave in Rome 44 years ago and which I mentioned at the beginning of this article (Fraser 1962a). *The complexity of the genetical dynamics of a population can be compared to the complexity of the molecular organisation of a cell. Yet just as a cell functions as a beautifully integrated whole so does the total genetical constitution of a population; and just as a cell is sensitive to a variety of insults, so is the hereditary material of our species to any uncontrolled changes in its environment.*

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STYLIANOS E. ANTONARAKIS

2. Genome and Postgenome: Present and Future Human Genome Variability and Disorders

One of the most important and crucial questions and challenges of modern medicine is to identify the genetic variation that causes or predisposes to the phenotypic variation. In simple terms the question is: what are the variants in the genomes of different individuals that are the molecular basis of human suffering from the myriad of common and rare disorders? This challenge is as old as medicine itself, but the recent completion of the DNA sequence[1] and on-going exploration of the human genome provides the means to a novel and powerful approach to advance our knowledge and provide some solutions to the medical problems.

The Human Genome Project and its functional elements

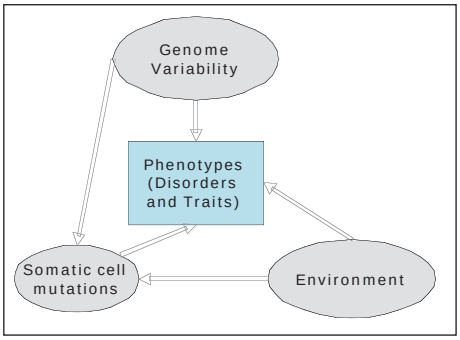
The international and collaborative human genome project[2] was initiated on October 1, 1990 after a period of intellectual gestation in the 80s. The goals of the project were to map, clone, and sequence the entire human genome. The project was essentially completed in 2004. The entire euchromatic (protein-coding) portion that accounts approximately for 93% of the genome has been sequenced to an accuracy of less than 1 error per 10,000 nucleotides. The remaining 7% that comprises the centromeric regions of human chromosomes, the acrocentric short arms, the distal chromosome Yp and the secondary constructions of certain chromosomes, collectively named the heterochromatic regions are still unknown. The total estimated length of the average human haploid genome is approximately 3,076,700,000 nucleotides. The sequence is freely available via public accessible databases, the so-called genome browsers (*http://genome.ucsc.edu/* and *http://www.ensembl.org/index. html*). Our knowledge of the functional elements of the human genome, however, is limited and considerable efforts are now being directed towards the identification of the important segments of the genome that are likely to be involved in health and disease. The present evidence suggests that there are no more that 25,000 genes in our genome (the human nomenclature database listed 23'413 gene names on 15 December 2005; *http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl*), but this number could be an underestimate.

The nucleotide sequence of additional mammalian and other genomes[3-5] suggested that approximately 5% of our genome is highly conserved among mammals and this could be considered as the lower limit of the functionally important genomic sequences.[3, 6, 7] It is also likely that additional genomic elements, not conserved in all mammals, are of functional importance. To that end, an international project named ENCODE (ENCyclopedia Of DNA Elements; *http://www.genome.gov/1000 5107*) has been launched by the National Institutes of Health, USA, to identify all functional elements of 1% of the human genome.[8] The overall goal is to develop and establish methodologies, so that all functional elements of the entire genome could eventually be identified.

Genome variation

Since the first identification of DNA polymorphisms[9] in 1978, numerous studies have so far revealed extensive sequence variability among individual human genomes. This polymorphic variability is such that each individual possesses a unique genome not shared by any other individual on earth (except for monozygotic twins). The most common type of variants are nucleotide substitutions (single nucleotide polymorphisms; SNPs). A public SNP database that lists all of these potential variants contains more that 10 million entries (dbSNP; *http://www.ncbi.nlm.nih.gov/ SNP/index.html*). It has been estimated that approximately 1 in 1,000 nucleotides differs between two randomly chosen human genomes. Thus approximately 3,000,000 single nucleotide variants paternal genome and maternal genome contribution for each one of us! This number is certainly an underestimate since it refers only to the common genetic

Fig. 1 - Individual genomic variability is an important contributor to the various human phenotypes. Somatic cell mutations contribute to the various neoplastic syndromes. The impact of the environment is also a key factor in the phenotypic expression. A major goal of genetic medicine is to identify the genomic variants that are responsible for the development of the various disorders.



variation. An international project has just been completed, named HapMap project,[10-12] the goal of which was to define the patterns of common SNP genetic variation in a sample of 270 DNAs from individuals of European, African, Chinese and Japanese origin (*http://www.hapmap.org/*). The data obtained in this project involve approximately 2.8 million SNP and our publicity available. The results of this project are likely to significantly contribute to the understanding of common and rare genetic disorders. The variability of human genomes is the underlying cause of the differential risk for the diverse human phenotypes and thus major research efforts need to be focussed on the discovery of the links between DNA variants and phenotypes.

Genomic variation is not only limited to SNPs. Other types of common variation are the short sequence repeats,[13] the copy number polymorphisms (*http://paralogy.gs.washington.edu/structuralvariation; http://projects.tcag.ca/variation*), the insertion-deletion polymorphisms, and the inversions of DNA. The functional significance, if any, of the majority of these polymorphic variants is unknown.

The "monogenic disorders"

The past 20 years have been triumphant for the identification of genes causing numerous monogenic mendelian disorders. A catalogue of these disorders, the genes involved, and the pathogenic mutations could be found in two databases, that of OMIM (online Mendelian Inheritance in Man; *http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM*) and the HGMD (human gene mutation database; *http://www.hgmd.org/*). The discoveries of alleles responsible for monogenic disorders increased our understanding of the molecular mechanisms that lead to phenotypes due to genome variants, but also introduced us into the complexity of gene-gene and genome-environment interactions. The most important lesson from the mendelian disorders was that even these "simple" disorders are also multifactorial and complex.[14] Issues such as genetic heterogeneity, allelic series, penetrance, modifiers of phenotype (environmental and genetic), digenic inheritance, triallelic inheritance, somatic mutations, uniparental disomy are phenomena that contribute to the complex interplay between our genomes and the environment.[15] The appreciation of these complications may unable us to form hypotheses for the understanding of complex, polygenic phenotypes. Furthermore, the mendelian disorders not only introduced us in the important and serious issues of presymptomatic diagnosis, and genetic screening, but also revealed the multidisciplinary ethical, legal and social aspects of genetic medicine.[16, 17]

Postgenome medical objectives for the next decade

It is obvious that our knowledge regarding the causes of the majority of common human disorders is in a primitive stage. Since the genetic contribution to almost all of these disorders (including cancers) is substantial (see figure for a schematic representation of the causes of disorders), the study of genomes of individuals with the various disease phenotypes becomes an absolute priority for medical reasons. Actually, all the exciting achievements and developments of the genetic research now provide a new knowledge infrastructure to attack the common and serious health problems.

Some goals for research related to genetic medicine include:

– Identify all the functional elements of the genome that are likely to be involved in health and disease.

– Discover the exact function of each portion of the genome.

– Discover all pathogenic, high penetrance mutations that cause genetic disorders.

– Identify all genomic variants that increase or decrease the risk for the complex, common, multifactorial phenotypes.

– Use postgenomic knowledge to introduce novel therapies.

– Use postgenomic knowledge to maintain the health capital of individuals and populations.

It is likely that the genomic information will have profound effects in all aspects of medicine, including the understanding of the mechanism, diagnosis, prognosis, and treatment of a large number of disorders.

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CLOTILDE MIRCHER

3.Congenital Illnesses Connected with a Chromosome Anomaly

Introduction

Chromosome anomalies are at the origin of a not negligible percentage of illnesses present from birth onwards. Such anomalies have grave consequences for early development in the womb, for the health of the child and the adult, and for his or her intelligence or fertility. Many advances have been made in terms of diagnostic possibilities and the medical accompanying of such illnesses. However, a radically effective treatment for these illnesses do not exist, even when the cause has been known for some time, as is the case with trisomy 21.

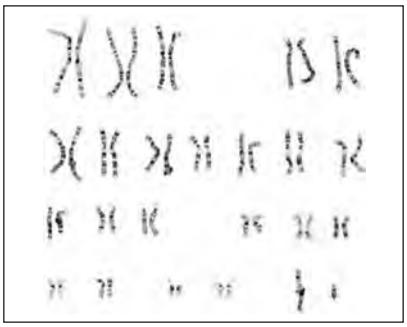
The Jérôme Lejeune Institute (JLI) was created in 1997 by the Foundation with the same name to treat patients of all ages afflicted by mental deficiency of specific genetic (chromosome or monogenic) origins, or where there is a strong suspicion of such origins, and to promote research not only of an epidemiological and clinical kind but also of a therapeutic character for these patients. Ever since its inception, about 3,500 patients from birth until over the age of sixty have been regularly supervised through multidisciplinary consultation. The majority of these patients (90%) had a chromosome anomaly. Basing myself on the experience of the Jérôme Lejeune Institute and the Jérôme Lejeune Foundation, this paper will address the existing prospects, or the prospects that have to be developed, for treatment, diagnosis and therapeutic research in relation to these illnesses.

Definition-Epidemology

The particularity of chromosome anomalies is that they involve various genes, both genes that are absent and surplus genes as well. In this they are different from monogenic illnesses which involve only one gene. Chromosome anomalies afflict two people in every thousand, and over a thousand syndromes have been described. 30% of chromosome anomalies are balanced and do not in general have consequences for the person who is the carrier but they may have consequences for his or her fertility or offspring. The other 70% are imbalanced and involve: anomalies of number (86%), trisomy or monosomy; anomalies of structure (inversions, deletions, duplications) (14%) derived by chance (3%) or by inheritance (11%). The consequences of these imbalanced chromosome anomalies are important because they are responsible for 8% of infant deaths, from 4% to 8% of congenital malformations, and from 12% to 35% of mental deficiencies. They also bear upon male fertility, and are responsible for repeated false pregnancies and for predispositions to certain types of tumour. The aneuploids are due to meiotic non-disjunction and their frequency is directly related to the age of the mother, except in the case of Turner's syndrome (45, X). The anomalies of structure also arrive at the moment of meiosis because of non-homologue rupture and reparation. The areas of the karyotype predisposed to these illegitimate recombinations are known about: it is estimated that the number of regions of the genome that are involved is 170, but at the present times only 30 illnesses connected with this mechanism have been identified. In children born through the use of medically assisted techniques of procreation there does not seem to be an increase in the frequency of chromosome anomalies. However, an increase in illnesses connected with a parental imprinting anomaly has been observed. Most of such autosomic anomalies involve a mental deficiency.

History and Techniques

The various stages of the history of knowledge about chromosome illnesses are closely bound up with the development of the techniques for the observation of human chromosomes. In 1912 de Wini-Warter studied human chromosomes but did not reach a final conclusion about the number of chromosomes of the human species. It was only in 1956 that Tijo and Levann improved the techniques of cell culture by adding colchicines. By blocking mitosis this allowed the chromosomes to be seen in a clearer way. This technical advance enabled Prof. Jérôme Lejeune[1] in 1959 to describe the first illness connected to chromosome anomalies – trisomy 21. This description would be followed by many others by his team and other groups in the world, in studies which centred around sexual or autonomous chromosomes. In 1960 an international conference established the first classification of chromosomes and numbered them in decreasing fashion from 1 to 22, 22, as well as chromosomes X and Y which are responsible for the determination of a person's sex.



It will be remembered that in 1866 G. Mendel established the laws of inheritance but it was only in 1944 that Averv stated that DNA was the support mechanism of inheritance and only in 1956 that Watson and Crisk established the double helix structure of DNA. The mutilation of DNA, which was only described very recently (1985), opened up new prospects for the explanation of new chromosome illnesses connected with a parental imprinting defect. In 1970 de Grouchy, Lejeune and Dutrillaux created new techniques (warming, the use of papain) which allowed the obtaining of alternatively bright and dark bands whose distribution in every chromosome allowed chromosomes to be described in a more effective way. The number of bands obtained defined the resolution of the karyotype. At the present time karyotypes (high resolution) can be obtained from 700 to 1,000 bands.

Classic cytogenetics is presently linked to the techniques of molecular biology (*in situ* hybridisation of fluorescent tubes (FISH) specific to a precise region. These methods allow, from a clinical point of view or in a more systematic way, to look for micro-rewritings that are not visible even using his resolution techniques). Lastly, new promising techniques have appeared: the techniques of hybridisation of fluorescent tubes on DNA molecules stretched out on, and fixed to, blades. The technique of comparative genomic hybridisation (CGH) studies in a global way the menome of the patient and allows the identification of an imbalance of from five to ten megabases. The development of CGH-arrays (on fleas) allows a better resolution (0.5 to 1 Mb) to be expected because they are swifter and more systematic.

Diagnosis

Even though the percentage of mental deficiency and congenital malformations whose aetiology is not known remains important, the constant development of such techniques, which are always associated with a clinical analysis (genealogical tree, family and personal precedents, examination of the child), has allowed diagnosis to be improved markedly. This is important for the child itself because it allows the illness to be given a name and to avoid diagnostic errors, which, indeed, are the source of great suffering for the parents. Great knowledge of the illness is indispensable, not least for the prevention of further handicaps which can alter in a significant way the lives that people lead.

Diagnosis also allows genetic advice to be given to the parent, reassuring them about the chance character of the anomaly and, in contrary fashion, informing them about the risks that other future children of theirs could run. Such genetic advice is also crucial for the rest of the family, above all else for siblings who are of the procreative age. It is calculated that it is necessary to do genetic analyses again about every five years in the case of

unexplained mental deficiency given the constant advances that are taking place in the techniques of diagnosis. However, as has already been observed in this paper, the improvement in the techniques in this field should always be primarily of utility to the child. Indeed, there is a great temptation to use these techniques to engage in a systematic identification of illnesses within the population in order to eliminate the birth of children who are the carriers of such illnesses: for reasons of 'compassion' but above all else for economic reasons. The increased life expectancy of people who are mentally retarded, like the increased life expectancy of the rest of the population, is held to generate costs that are not seen as having a priority importance. The proposed systematic identification of trisomy 21 is discussed at the present time in some countries and the new techniques, once they have been created and tested, could be used to identify in a systematic way all foetuses that are carriers of micro-rewritings. To give an example: with the current techniques of prenatal identification of trisomy 21 the level of medical interruptions of pregnancy for this illness is much higher in regions where prenatal identification is suggested in a significant way (Ile de France 79.7%; Barcelona 72.6%), compared to those where this policy does not exist (the northern region of Holland: 23.7%; the southern region of Portugal: 31.7%).[2] Such policies raise the question of the role mentally handicapped people should have in certain industrialised countries. Some countries do not have policies involving the systematic identification of trisomy 21 but have instead a vigorous policy to provide help to families that have to face up to the suffering that it involves (financial help, schools, special centres, help at home, etc.). Lastly, a systematic policy of prenatal identification makes the acceptance of handicapped children by their families even more difficult. A French study[3] showed that 22% of children with trisomy 21 born in the Paris regions between 1980 and 1989 were abandoned at birth. In our experience, of 263 patients with trisomy 21 that were abandoned and monitored by the Jérôme Lejeune Institute (JLI), only two were born before 1980. The others were born after that date, the time when a more systematic process of prenatal identification was begun in France.

Medical Accompanying

The importance of diagnosis in order to allow children to benefit from the advances in medicine has already been stressed in this paper. One of the roles of the JLI is specifically to propose to patients during their lives a medical accompanying that is suited to their age and their illness in order to identify and treat the various complications that may emerge. Some of these complications are supplementary handicaps that gravely alter, at times, the quality of life of patients. I would now like to provide some significant examples of this.

– *Trisomy 21* is responsible for mental deficiencies of various degrees of intensity. Potentially, a rather large number of complications are associated with this syndrome, most of which can be foreseen or corrected through appropriate treatment. West's syndrome is a form of epilepsy that emerges between the age of five and fifteen months, more or less. Its frequency is 1% in trisomy 21 but 0.3% in the population as a whole. Its diagnosis can be delayed because of a low expression of symptoms (bending spasms, arrest of psycho-motorial development or regression). However, diagnosis is easy with an electroencephalogram and the treatment for it is well codified and effective. A recent study[4] on a number of children with trisomy 21 showed that a delay in diagnosis and in treatment for more than two months was linked to a lower IQ and to the presence of autism in the children who were afflicted with the syndrome. Knowledge of this complication and its identification can have a very important impact on the health of the child involved and on the whole of his or her family.

– *Willi Prader's syndrome* is responsible for a forms of mental deficiency of varying degrees of intensity, associated with abnormal eating behaviour (bulimia) – the cause of obesity which becomes established from the age of two onwards and which is subsequently responsible for other medical disturbances. An early and multidisciplinary examination of the child and the family (dietetics, endocrinology, psychology) allows a real prevention of such obesity. At the JLI the youngest patients, if monitored well, have a controlled corporeal mass index (<20). In this they are different from older patients who have not benefited from such prevention (IMC>40, which corresponds to greater obesity).

– *The 'cri du chat' syndrome* is due to a deletion of the short arm of chromosome 5. Half of these patients are unable to speak and often have behavioural disturbances that require psychotropic forms of treatment. However, in the face of a behavioural disorder an attempt will also be made to find a somatic pain: of an orthopaedic kind (high frequency of scoliosis) or digestive character (hiatus hernia with gastro-esophageal backflow). These complications, in fact, are more frequent in this illness and should not be neglected in patients who are unable to express themselves.

Research and Treatment

Although it is possible to prevent and treat a large number of the complications of these illness, for the moment there are no forms of treatment for mental deficiency in these chromosome illnesses. However, there are various different ways of approaching this difficult subject:

– *The genetic path*, which is the most logical: knowledge about genes and their function should allow the drawing up of rational therapeutic strategies both through classic pharmacology and through new techniques (gene therapy, interferent RNA). For the moment, although good cell and animal models of the most frequent chromosome pathologies exist, the therapeutic pathways are still modest and much still remains to be done in order to understand these illnesses well, illnesses which involve the role of a large number of genes, both genes that are absent and surplus genes.

– *The clinical path*. Two examples may be given:

a. The Smith-Magenis syndrome is due to a micro-deletion in 17p11.2. In addition to mental deficiency, one may also observe in these patients sleep disturbances, and character and behaviour disturbances, which make daily life especially difficult. The existence of these sleep disturbances have led medical doctors (Dr de Leersnyder-Necker- Parigi) to study the melatonin cycle and to discover an inversion of the circadian rhythm of this hormone, which is necessary to sleep. A treatment that blocks the daily secretion of the hormone, and the support of melatonin in the evening, has enabled these children to regain a more regular rhythm of sleep and thus to engage in learning with greater success.[5]

b. In trisomy 21 there are various factors that foster the emergence of sleep apneas (anatomical particularities, a greater frequency of ORL infections, central apneas, being overweight). In the absence of complaints on the part of the patient, the diagnosis can be delayed or omitted. However, a chronic sleep apnea can have grave consequences in the short term for growth, learning and behaviour amongst the very young. In the case of adults it can alter attention, memory, and be responsible for mood and behaviour disturbances. In the long term, a chronic lowering of arterial oxygen saturation is deleterious at a cellular level, and for the neurons in particular. A syndrome of sleep apnea that was unknown for many years could be the cause of early aging and cognitive regressions observed in 50% of trisomy 21 patients over the age of fifty. The treatment is not simple but takes the form of certain preventive measures. For some patients one could try to use equipment for positive pressure ventilation which could allow a maintenance of the cognitive functions and in part prevent this cognitive regression which is so catastrophic. In these two examples one can see that even without knowing all the genetic mechanisms and without aiming at the genes themselves one can improve or preserve the cognitive functions of patients.

– *Exchange between fundamental research and clinical observation* is indispensable and very productive in advancing both field and finding therapeutic pathways.

- Knowledge about the genes of chromosome 21will lead, for example, to useful information, that is to say technical advances, for other illnesses such as tumours (increase in the frequency of forms of leukaemia and a decrease in solid tumours in trysomy 21) or Alzheimer's disease.

- Another example of such synergy between clinical work and research is interest in the CBS (cystathionine beta-synthase) gene: Jérôme Lejeune compared, in order to contrast them, the clinical signs observed in trysomy 21 and in homocystinuria, an illness linked to a lack of the CBS enzyme. In 1975[6] he deduced from them the localisa-

tion of the coding gene for this enzyme on chromosome 21. This localisation was confirmed in 1985/7) in 21q22.3. The next stage was to think that this gene played a greater role in mental deficiency present in trisomy 21 patients. The JLI (Dott. H. Bléhaut) has for a year now been engaged in the CIBLES 21 research programme which is intended to create an inhibitor of this enzyme in order to normalise its activity, which is heightened in trisomy 21.

Other Prospects

– Foetal medicine: if a treatment were shown to be effective, the most logical thing would be to propose its use on a foetus in the womb. Prenatal diagnosis could thus offer this young patient the benefit of the advances in research.

– Prevention: lastly, taking into account the difficulties of research, prevention, where possible, would certainly be the best 'therapy'. The only real prevention is that which seeks to impede the conceived child from being a carrier of a chromosome anomaly and not the organisation of a systematic identification within the womb so as to then propose the eliminated of affected foetuses. Even though one does not know the exact cause of the emergence of chromosome anomalies, the age of the mother is certainly a risk factor. In a recent study (EUROCAT),[2] it was observed that the prevalence of trisomy 21 (live births + foetus deaths – medical interruption of pregnancy) varies a great deal from country to country and is directly linked to the age of pregnant women (3.72% in Ile-de-France where pregnant women are the most advanced in years, as against the 0.94% in Portugal). A public health campaign directed towards informing people and in particular women about this risk factor could be an effective means of prevention, always in a way that respects individuals.

Conclusion

In recent years we have witnessed a large number of technical advances in the field of diagnosing chromosome illnesses. The use of such techniques can or cannot be beneficial to patients. Recent years have also witnessed significant improvements in medical accompanying with a real prevention of associated handicaps. More effective forms of treatment remain to be found. The first step is hope, that is to say to believe that it is possible to find them ('we will find them; it is much easier at an intellectual level to find a treatment for trisomy 21 than it is to send a man to the moon', observed Prof. J.L. Lejeune). This is also a matter of justice for all those patients afflicted at the level of their intelligence. Like all sick people they have the right to a decisive and effective research effort.

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PIETRO CHIURAZZI

4. Monogenic Illnesses

Monogenic illnesses are due to alterations in the DNA sequence within individual genes, the fundamental units of hereditary information contained in the nucleus in each one of our cells. These alterations (or mutations) are not generally visible in an examination of chromosomes because they may involve a few nucleotides, that is to say the 'letters' of DNA, and each chromosome is made up of tens or hundreds of millions of nucleotides. The mutations and the corresponding genetic illnesses can be transmitted to the next generation following the laws of heredity described by Gregor Mendel in 1865, well before the discovery of chromosomes and DNA.

The nucleus of every cell in the human body contains forty-six chromosomes made up of hundreds of millions of nucleotides (adenine, cytosine, guanine and thymine), making up a total of three milliard 'letters' of deoxyribonucleic acid (DNA). Although the sequence of human DNA has been determined almost completely, the number of genes is still uncertain and oscillates between twenty thousand and thirty thousand. This uncertainty is the result of the fact that genes are 'fragmented' and dispersed along the genome. Just as in the case of atoms a lot of empty space separates the electrons from the protons and the neutrons from the nucleus, so only 3% of the DNA is effectively used to direct the synthesis of the proteins which animate the life of the cell. In fact, one of the two filaments of the DNA in order to carry out its function must first be 'recopied' (or transcribed) into a single filament of RNA (ribonucleic acid) which is then transferred from the nucleus to the cytoplasm of the cell and is 'transformed' (or translated) into the corresponding protein.

To summarise: 1. the genes are the fundamental units of hereditary information (to which is given the overall name of the genome); 2. they are written with the four letters or nucleotides (A,C,G,T) of the deoxyribonucleic acid (DNA) which is distributed in forty-six chromosomes and is conserved in the nucleus of the cells; 3. the genes (which are about twenty-five thousand in number) must first be transcribed into ribonucleic acid (RNA) and then translated into proteins in the cytoplasm. The DNA may be compared to a book that contains all the music of the cell, the messenger RNA is like the musical scores that are printed for the musicians, and the proteins correspond to the music that is actually played; 4. the proteins direct the life of the cell and can have a structural function (constituting the framework of the cells) or an enzymatic function (being able to transform one molecule into another). Lastly, it is important to remember that all the genes, like all the chromosomes in which they reside, are present in two copies (one coming from each parent).

The human genome project, conceived of some twenty years ago, has allowed the achievement of the objective of determining the sequence of three milliard nucleotides of human DNA. This result, which was announced in the year 2000 and published for the first time at the beginning of 2001 in the prestigious journals *Science* and *Nature,* may be considered to have been achieved a level of 90% but this does not mean that all the fragments of DNA that are the genes have been identified. More than a half of all genes lie unexplored in the sequence of our genome which still has to be completely decodified. In addition, we have information that is still very incomplete about the functions performed by the corresponding proteins in the various (muscular, nerve, epithelial etc.) cells. The information derived from the human genome project, which thus continues to accumulate at an exponential rate, are contained in data banks such as that of the American National Center for Biotechnology Information (*http://www.ncbi.nlm.nih.gov*) or that of the European Bioinformatics Institute (*www.ensembl.org*). Through these data banks it is possible for all researchers, or even only the curious, to explore the great book of the genome of our species. In addition to the human genome, the genomes of various species of vertebrates (mouse, chimpanzee), invertebrates (fruit fly, worms) and single cell organisms (beer yeast, various microbes) have also partly or totally sequenced.

By way of example, we may explore the human genome thanks to the EnsEMBL data base (*http://www.ensembl.org/Homo_sapiens/index.html*), beginning with the chromosome map on the first page. When clicking, for example, on chromosome X, a screen appears which portrays the chromosome with its cytogenetic bandaging with beside it the density of genes for each sub-region. The genes on chromosome X are about a thousand in number. When clicking on one of these regions it is possible to visualise the genes that are in that region at different levels of focus. These genes are separated from each other by hundreds of thousands or even millions of nucleotides. When one increases the zoom one can perceive the fragmentation of genes which are composed of various portions called 'hexones' which are to be found in the 'score' of the messenger RNA to be translated into protein, interrupted by sequences that are generally longer (the so-called 'introns') which are eliminated by the RNA after being recopied by the DNA. The phenomenon of the elimination of the introns (a process termed 'splicing') also allows different RNA messengers (which correspond to different proteins) to be

obtained, with the inclusion or the exclusion of certain hexones in the mature RNA. Lastly, at the greatest level of zoom, we find the sequence of the nucleotides of the DNA in that particular tract of the human genome. This sequence is written on both the filaments of DNA in a complementary way with an 'A' in front of every 'T' and a 'C' in front of every 'G', as was posited by Crick and Watson in 1953.

In the following table is listed the length in pairs of nucleotides of each chromosome and the number of presumed or confirmed genes that are located on that chromosome, for a total of about 3.1. milliard nucleotides and 22,531 total presumed genes. The number of genes correlates roughly with the length of the chromosomes.

chromosome	length (bp)	genes (known+new)	known genes
1	245,522,847	2281	1988
2	243,018,229	1482	1246
3	199,505,740	1168	1033
4	191,411,218	866	743
5	180,857,866	970	834
6	170,975,699	1152	1050
7	158,628,139	1116	916
8	146,274,826	794	692
9	138,429,268	919	778
10	135,413,628	862	730
11	134,452,384	1426	1264
12	132,449,811	1104	1009
13	114,142,980	399	318
14	106,368,585	733	646
15	100,338,915	766	589
16	88,827,254	957	839
17	78,774,742	1257	1104
18	76,117,153	322	267
19	63,811,651	1468	1337
20	62,435,964	631	592
21	46,944,323	271	243
22	49,554,710	552	471
X	154,824,264	931	766
Y	57,701,691	104	76
	3,076,781,887	**22,531**	**19,531**

The human genome has about two metres of double helix DNA, more or less closely enveloped in proteins called hystones to form chromatin. Normally, the DNA is partially unwound in the nucleus of the cells and has the appearance of an indistinct ball but when the cells have to divide the genome folds back onto itself to the utmost in an ordered way and becomes visible in the form of chromosomes. Forty-six chromosomes characterise the human species in the form of pairs, with twenty-three coming from the father and twenty-three coming from the mother. The commonest way by which the cells divide is through the process of mitosis. This division produces an entire organism beginning with the first fertilised egg cell or zygote. Each cellular division pre-supposes the replication of the DNA so as to assure that every daughter cell has a complete copy of the genome. At the beginning of mitosis each chromosome is made up of two identical chromotides which are united by a centromere and such chromotides separate in an ordered way to end up with forty-six chromosomes in both the daughter cells. Each chromosome now has only one chromotide.

During the replication of the DNA errors can occur and erroneous nucleotides can be inserted. These errors, otherwise known as mutations, will then be found in the daughter cells and can also be transmitted to the next generation, causing a monogenic illness. In order to be transmitted to the next generation the mutations must be present in the specialist cells entrusted with fertilisation and thus the formation of the zygote. These cells, known as gametes (ovule and spermatozoon) form through a special cellular division known as meiosis which reduces the number of chromosomes by a half (from forty-six to twenty-three), allowing the ordered segregation of the homologue chromosome (i.e. the members of each pair). The new individual, in fact, will receive twenty-three chromosomes from each parent and will have forty-six chromosomes once again.

During meiosis, as in the case of the homologue chromosomes, the pairs of each gene (alleles) also separate and take the form of separate gametes. This is the biological basis of the law of the segregation of the alleles discovered by Mendel. Each allele has a 50% chance of being included in the gamete that will generate the zygote of the child. Mendel had also observed that in hybrid plants, that is to say heterozygotes made such because of two different alleles (which for example lead to the production of yellow or green seeds), one of the alleles is dominant and determines the phenotype, whereas the other allele is recessive. A recessive allele determines the phenotype only when it is present in two pairs and the individual is a homo-zygote.

Applying the observations of Mendel to medical genetics we can say 1. that monogenic illnesses are brought about by mutations in an individual gene and by the matching protein defect; 2. that a mutant gene can arise in the production of an anomalous protein or no protein; 3 if a mutant allele determines the phenotype when it is present in a single pair as well it is dominant; 4. if a mutant allele determines the phenotype only when it is present in a double pair it is recessive.

In a typical genealogical tree that demonstrates a dominant transmission, a characteristic (or an illness) is transmitted from the parent to the child in a vertical way through the passing on of a single allele. The risk of transmission is 50% and most of the individuals affects are hetero-zygotes with a mutant allele and a normal allele (Aa). In the case of a recessive transmission, on the other hand, only the individuals who are homo-zygotes because of this mutation will be affected by illness (as in the case of the children of close relatives) or composite het-

ero-zygotes who are such because of two different mutations but of the same gene. The hetero-zygotes in this case will be healthy carriers and will run a roughly 25% risk of having sick offspring.

A special case is that of the transmission of X-linked characteristics, that is to say characteristics dominated by mutations in genes on the chromosome X, present in two pairs in women (XX) and in a single pair in hemi-zygote males (XY). In the case of recessive X-linked transmission, indeed, women who are hetero-zygotes because of this mutation are healthy carriers whereas 50% of their male children will be affected by illness. In X-linked transmission one never observes a transmission from male to male, precisely because the father transmits the chromosome Y to his male children. All the daughters of a sick male, on the other hand, will of necessity be carriers.

For monogenic illnesses as well there exists an up-to-date data bank on Internet – OMIM (Online Mendelian Inheritance in Man). The OMIM can be accessed through the site of the NCBI and catalogues practically all of the genetic conditions involving (monogenic) Mendelian transmission described in the literature in the field. In the ONMIN at the present time are listed or described at levels of varying detail about ten thousand genes with their corresponding mutations and corresponding genetic illnesses. For each gene and/or condition there is a brief historical description, the presentation of clinical characteristics and of a number of the principal mutations with the corresponding phenotypes (illnesses). In addition, the most important bibliographical references are also cited.

It is important to remember that the clinical expression of monogenic illnesses can be extremely varied (from light to very grave). At times this difference can be explained by the presence of different mutations of the same gene. At other times the same mutation can involve very varied clinical pictures and this can be explained with reference to the modifying action of other genes and the corresponding proteins. Indeed, no protein acts in an isolated way.

When we speak about the heterogeneousness of alleles, on the other hand, we refer to where the mutations (which are generally different) of the same gene bring about four absolutely different clinical situations. At times this can be explained with reference to the effect of the mutation on the activity of the protein (the acquisition rather than the loss of a function) and in other cases it is possible that there is an alteration of the splicing which brings about the production of a protein in a different part. A classic example of the heterogeneousness of alleles is provided by mutations in the gene and the receptor because of the fibroblast growth factor FGFR3. These mutations can be responsible for clinical situations that are totally different, such as skeletal dysplasias without the involvement of the cranium, craniosynostosis or even a dermatological pathology.

Lastly, we should bear in mind that many monogenic illnesses have a heterogeneousness of locus (or genetic heterogeneousness). In

this case we should remember that many proteins can be required for a particular cellular function and thus mutations in more than one gene can cause the same phenotype (illness). When mutations in more than one gene at the same time are necessary to bring about a genetic illness we can speak about polygenic or multifactorial heredity (however much particular environmental factors may also be necessary).

The detailed description of the metabolic paths and the molecular mechanisms of the normal functioning of cells is a preliminary precondition to understanding the mechanisms that bring about genetic illnesses and the identification of possible effective therapies. The example of phenylketonuria, a well known recessive monogenic illness that is looked for at birth in all new born children, is particularly instructive. Most of the patients with this illness, indeed, have mutations of the gene of phenylalanine hydroxylasis (PAH) which normally converts the essential amino acid phenylalanine into tyrosine. The phenotype can vary from the grave form of classic phenylketonuria to benign hyperphenylalaninias (which take varying forms). In some cases, instead, mutations are present in genes that codify the enzymes that are entrusted with the synthesis of a co-factor that is indispensable for the reaction, the tetraidrobiopterine (BH4). This is a typical example of genetic heterogeneousness. Lastly, the levels of phenylalanine that are ingested with a person's diet greatly condition the phenotype effect, influencing a multifactorial illness in which the effect of the gene mutations can be almost eliminated by a lack of phenylalanine in the diet. This observation forms the basis of the dietary treatment of classic phenylketonuria, whereas the tetraidrobiopterine deficit is not a matter at all of diet. In these cases the BH4 deficit also inhibits the working of other enzymes such as hydroxylase tyrosine and hydroxylase triptophane, which are fundamental for the synthesis of the dopomin and serotonin neurotransmitters, requiring a different (but still unsatisfactory) therapeutic approach.

In conclusion, knowledge about the tens of thousand of human genes will contribute to the identification of many monogenic illnesses derived from Mendelian transmission. A description of the mutant proteins and their natural and pathological function in the complex network of the molecular interactions of the cell is the next difficult but necessary step to achieve the possible identification of effective therapies. As is demonstrated by the example of phenylketonuria, knowledge about the pathogenetic mechanism can suggest therapies that are easier than the replacement of the defective gene by a normal pair. Gene therapy, in fact, is still a not very realistic option and constitutes a formidable technological challenge.

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MAURIZIO GENUARDI

5. Multi-factorial Diseases

Multi-factorial diseases are pathological conditions created by complex interactions between genetic factors and environmental factors. In general it is believed that the genetic factors, like the environmental factors, that are involved in the pathogenesis of these conditions are many in number. Specifically because of the causal mechanisms and the multiplicity of genetic factors that are involved, these conditions are also called 'complex' or 'polygene' diseases. The completion of the human genome project has opened up prospects that were unimaginable until two decades ago. This project has led to the fact that these conditions have today become the subjects of intense study in the field of the biomedical sciences and have provided the methodological bases for the launching of ambitious projects on a vast scale directed towards identifying the genetic and environmental factors that are involved.

This group of pathologies is distinguished from traditional genetic diseases caused by defects in individual genes because of the modalities by which they express themselves in families. In the case of classic (or monogene) genetic diseases one can observe the involvement of different members of the same family, and an examination of the number of individuals affected and their degree of kinship in a congruous number of families allows the way in which the genetic transmission of the malady takes place to be determined. For example, in the case of a dominant autosomic illness most of the families analysed demonstrate the direct transmission of the illness from parent to child and the presence of more than one generation of individuals who are afflicted by the malady. In contrary fashion, in the case of multi-factorial diseases the situation that is most frequently encountered is that of the presence of a single case of the malady within the family. In a fraction of families in which a multi-factorial condition is present two affected individuals exist, often closely related to each other, or, more rarely, there are three or more individuals who have the illness. This kind of situation could be caused by factors that are purely a matter of chance, above all in the case of diseases that are common within the population as a whole. The involvement of genetic factors is demonstrable when the illness appears more frequently in the relatives of patients as compared to the general population. Epidemiological studies of this kind measure the l level, that is to say the relationship between the incidence of the disease in a specific class of relatives of individuals with the illness as compared to the population as a whole. The class of relatives that is most frequently subjected to examination is that of siblings. In the case of a classic Mendelian illness, such as cystic fibrosis, the l level of the siblings – defined as ls, where s = siblings – is very high, being equal to 1 in 625. This means that the disease is 625 times more frequent in the siblings of a person already afflicted with the disease as compared to the general population. This also means that the risk of a sibling of a patient with cystic fibrosis developing the same malady is 625 times higher than is the case with a member of the general population. The same calculation as regards risks made for insulin-dependent diabetes or youth diabetes (type 1 diabetes) has a ls level of 15. This level is much lower than that involved in cystic fibrosis, given that when analysing families with cases of type 1 diabetes one finds that in most cases the malady is confined to one individual alone. Multi-factorial illnesses are thus characterised by ls levels that indicate a higher risk that the illness will appear in the relatives of affected individuals, even though these levels are lower than those to be observed with monogenic diseases.

In an attempt to explain the reasons for family aggregation in multi-factorial conditions different theoretical models have been proposed. In general terms they posit that a multi-factorial condition is caused by a definite number, which can be very broad and perhaps involve a few hundred, of gene variations in different locations. Each of these locations can take various forms, each one of which confers a different level of susceptibility or resistance to the development of the illness. The appearance of the illness takes place when there is a concomitance of genetic combinations and of exposures to environmental factors that rise above a certain threshold of susceptibility, above which the expressions of the illness begin to appear. There is no single combination, differently to what happens as a rule in the classic genetic illnesses; indeed, the illness can appear in individuals who have combinations of genotypes and of environmental factors at risk that are very different.

One of the reasons why today we are witnessing such a notable increase in the study of multi-factorial diseases on genetic bases lies in the fact that in this class of pathologies most of the common illnesses of man are included. These illnesses, of course, constitute the major source of outlay in socio-economic terms. For example, diabetes has a multi-factorial origin, as do arteriosclerosis and tumours. Compared to Mendelian diseases such as cystic fibrosis, b-talassemia and Duchenne's muscular dystrophy, whose incidence, with the exception of certain special geographical areas, is lower than one in every 2,000, these diseases are, in differ-

ent fashion, very frequent. The risks of illness generated by genes involved in the last pathologies are very high, often 100% or thereabouts in the carriers of causal genetic alterations. There are also hereditary forms of common illnesses. For example, it is well known that in a small fraction of tumours, such as breast cancer of ovary cancer, susceptibility to their development can be transmitted in a Mendelian way. One of the genes involved is called BRCA1, and confers a risk of between 40% and 80%, depending on the different cases analysed, of developing tumours during a lifetime. The relative risk expresses the relationship between the absolute risk of illness in the class of carriers of special genetic variants as compared to the population as a whole. This risk is thousands of times higher in carriers of genetic mutations that cause rare illnesses such as cystic fibrosis or Duchenne's muscular dystrophy. It is lower (of levels between five and ten), but always of a significantly high level, in the case of the BRCA1 gene and breast/ovary cancer, and this difference is due to the fact that this illness is already very frequent in the population as whole, where the majority of cases are not linked to mutations that act by means of a Mendelian mechanism. In multi-factorial illnesses the risk levels are often much lower, as in the case of the MTHFR gene and of defects in the neural tube (relative risk 2-4), even if the genetic factors of susceptibility identified hitherto are probably those with greatest influence and thus can be very high, as occurs with a special combination of genes of the HLA system in insulin-dependent youth diabetes.

The prevalent theory on the pathogenetic mechanisms of multifactorial illnesses holds that susceptibility to their development is caused by common or relatively common gene variants, differently to what takes place in the Mendelian illnesses where the gene variants involved are rare or very rare. The variants involved in multifactorial diseases belong to the category of genetic 'polymorphisms', that is to say those variations in the DNA sequence that have an incidence in the general population that is higher than 1%. In recent years, a special type of genetic variant has taken on a predominant role in the study of multi-factorial illnesses. I am referring here to the so termed 'single nucleotide polymorphisms' (SNPs) which involve the substitution of a single base of the human genome. For example, a hypothetical sequence AGGTGTC in a specific position of the genome could exist in the AGGAGTC form in some individuals. The substitution of the thymine (T) base with an adenine base (A) in the fourth position of the sequence would in this case constitute an SNP. It has been calculated that in the human genome an SNO is present every 290 sequence bases – given that the human genome contains about 3 milliard bases, this would mean a total of 10 million SNPs spread throughout the human genome in different positions. The SNPs have the great advantage of being employed in automatic analysis and this can be used in studies on a large scale. For

this reason, the discovery of an enormous number of SNPs, which has taken place thanks to certain collateral consequences of the human genome project, has given rise to the possibility of overcoming the numerical and technological limitations that have traditionally obstructed the development of projects aimed at establishing the genetic bases of multi-factorial illnesses.

Traditionally, the potential involvement of genetic polymorphisms in the genesis of multi-factorial illnesses is examined through association studies. These are rather simple investigations from a conceptual point of view which involve the identification and the comparison of the frequency of one or more variant examined in a series of cases made up of subjects affected by a specific condition with a series of control cases not affected by the pathology under study. When, after an application to engage in appropriate statistical tests, the frequency of a variant is significantly higher in the chosen cases than in the control cases, the association is defined as being positive. This indicates that the variant under study is probably involved in susceptibility to the illness. An example of an association study with a broadly positive result is the investigation carried out in 2001 by a group of French researchers on patients with Crohn's disease, an inflammatory malady of the intestine. This study revealed a significantly higher incidence of variants of a gene called CARD15 in subjects with Crohn's disease compared to the control group that was examined. In contrary fashion, the same study did not reveal any difference between control individuals and patients afflicted by ulcerous rectocolitis, a cousin illness of Crohn's disease, from which it is different because of certain clinical divergences. The frequency of three specific variants of the CARD15 gene was equal respectively to 29% in patients with Crohn's diease, 7% in the control subjects, and 5% in the sample of patients with ulcerous rectocolitis. The different between 29% and 7% was highly significant from a statistical point of view. Observation of a lower incidence of variants in the cases with ulcerous rectocolitis might lead one to think that these genetic polymorphisms even have a protective effect as regards this illness. However, it ap-

pears clear that there is no great divergence between the 7% and 5% levels, and indeed this difference does not appear to be relevant when subjected to statistical analysis.

In reality, the association studies are very often subject to a series of problems or errors. The data obtained on Crohn's disease constitute one of the few examples of results obtained in recent years that have stood up to further studies designed to reproduce such data in other case studies. The vast majority of positive associations described in the scientific literature in this area have not been reproduced by other studies. The simplest explanation for these discrepancies should be looked for in errors at source that may be rooted in the small number of cases examined or in the use of inadequate statistical methods. In general, association studies that have been carried out hitherto have been inadequate as regards the discovery of genetic variants with weak effects, that is to say variants that bestow relative risks lower than 2. Knowing about these matters, today it is possible to attempt to solve them, or at least partially, by applying rigorous statistical analyses, by analysing high numbers of samples, indeed thousands at the least, and by engaging in other precautions. Various studies now underway have been organised in this way and these envisage as a first step the collection of high numbers of samples. Amongst these studies reference may be made to the UK Biobank which will involve about 500,000 people over the next few years, the European study of twins, GenomEUtwin, which envisages the involvement of more than 600,000 sets of twins, and the studies on the populations of Iceland, Estonia and Australia. This last study envisages the study of two million people.

With the exception of the Icelandic project, these studies are still at their initial stages and have still not yet produced significant results: it is not possible to predict what their final outcomes and their consequences in terms of improving public health will be. At a general level, the technologies that are available, which it is assumed can improve substantially in the future, and the way in which the studies are organised, should allow significant results to be obtained. However, opinions on the utility of these studies vary in character.

There are those who argue that thanks to the identification of the genetic factors involved in multifactorial diseases that we will be able to achieve a personalised form of medicine. This is the vision that was formulated by one of the leaders of the human genome project, Francis Collins, in 1999. In a famous reading that was to become of notable relevance he presented the hypothetical data of a genetic check-up engaged in by an individual in the year 2010. On the basis of these results, the individual had an increased risk of contracting certain illnesses such as heart disease, colon and lung cancer, and a reduced risk of contracting Alzheimer's disease and prostrate cancer. Taking into account these elements, this person would be presented with measures designed to reduce the risk of heart disease and colon and lung cancer, and he could be advised to avoid subjecting himself to tests for prostrate cancer. It should be said that with respect to Alzheimer's disease any result, whether involving an increased or a reduced risk, would not have any consequence at a clinical level because at the present time there are no means by which to prevent this affliction.

The hyperbolic vision of Collins and other scientists envisages that through the analysis of the genetic profile of each and every individual one will manage to achieve a personalised form of medicine on the basis of the genotype and thus personalised forms of treatment. Pharmacogenetics, that is to say the study of the genetic bases of responses to pharmaceuticals, constitutes, in fact, a special and particularly promising field for the application of these methodologies.

However, there still exist a large number of doubts about the possibility of being able to achieve such a scenario, and the same may be said about the wisdom of applying possible future knowledge in this way. The power, that is to say the possibility of success, of the studies that are now underway is still something that has to be demonstrated, and this objection is substantiated by the fact that the number of genes that have been identified is very low. It is possible, indeed in the view of some people it is probable, that the genetic variants discovered in this way will not be able to substitute other risk markers that are widely used, such as, for example, cholesterol levels in the blood. Indeed, if genetic variants influence cholesterol level it would appear to be decisively more simple to dose this level. The effect of certain variants could be linked to the presence of environmental factors. In this case it would be preferable to reduce exposure to these, not least because these could also increase the presence of risk in those who are not carriers of genetic variants with which a interaction has been demonstrated. Lastly, as regards what has been said above as regards Alzheimer's disease, one may ask what utility knowledge of the risk level in relation to non-preventable illnesses could have. In such cases, indeed, such knowledge could have damaging effects from a psychological point of view.

The other scenario, which I would call the minimalist scenario, envisages that one can achieve knowledge about a certain number of genetic factors which have only a weak effect on susceptibility to multi-factorial conditions, but that only a limited fraction of these would lead to an improvement in basic knowledge about the mechanisms of the illness and, in the final analysis, to the development of new therapies, with benefits thereby accruing to public health.

Given present circumstances, and given that one cannot predict which of the two scenarios will come about, it is nevertheless important to ensure that the 'hyperbolic' vision does not prevail, above all so as not to foster illusory business based upon data that have not yet been verified and which could nourish and be nourished in a vicious circle of an excess of expectations regarding the possibilities of 'improving' the health or even the characteristics of the human species.

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6. Genetic Predisposition to Cancer and Latent Diseases

INTRODUCTION

When we see the sky grow dark on the horizon we say because of our previous experience – 'it's going to rain'. When we see a tree in flower in the spring we say – 'that will have a lot of fruit'. In the same way, when geneticists find a morbid genetic mutation in a new born child they make the following prediction – 'this child will develop this latent hereditary illness or this cancer when it has this age'.[1-2] But who knows how many black clouds have not produced rain, or how many trees have not kept the promise of their blossom? How many people predisposed to a pathology have not died, thanks be to God, because of this genetic predisposition?

In this age of molecular genetics we now know that tumours emerge following the mutations of certain genes that take part in the control of the processes involving: cell growth; the limitation of cell proliferation; the repairing of damaged DNA. In this paper I will address one after the other: 1. the definition of genetic predisposition to cancer and latent diseases; 2. the molecular mechanisms of predisposition to cancer; examples of DNA mutation that lead to a predisposition to genetic diseases.

I. THE DEFINITION OF GENETIC PREDISPOSITION TO CANCER AND LATENT DISEASE

Predisposition refers to the fact that an individual has a genetic inheritance that makes him or her susceptible during his or her life to developing a genetic disease such as, for example, renal polycystosis, Gaucher's disease, haemochromatosis, Duchen's muscular dystrophy, or hereditary cancer – retinoblastoma (RB), breast cancer (BRCA), and hereditary non polyposis colon cancer (HNPCC), etc.

1. Genetic predisposition to cancer

A woman who is a carrier of a mutation of the BRCA genes runs a risk of having breast cancer that is eight to ten times higher than is the case with the population as a whole, and a forty times higher risk of contracting cancer of the ovaries. There are also predispositions linked to the environment and lifestyle. Today, we know that only 5% to 10% of tumours are hereditary and transmittable (genetic mutations in the germinal line); that family cancer usually involves a cancer in more than one member of the same family even though it is necessarily hereditary; and that these kinds of cancer are sporadic.

1.1 History

At the beginning of the twentieth century, in essential terms, there were two lines of research in cancer studies:

1.1.1a. One of these lines explored the infectious basis of tumours and achieved the identification of the proto-oncogene and the oncogenes.

1.1.1.b. The other was based upon the correlation between the development of a tumour and cancerogenous and gene-mutating activity of a large number of chemical and physical agents. The work of Alfred Knudson belonged to this second line of research. He was the first to develop a theory that explained genetic predisposition to cancer by taking into account the multi-stage nature of the mutational process underway in the genesis of cancer. In families with a number of cases of cancer one of these mutations can be present from conception and this is be found in all the cells of the organism. In this case, given that a mutation is already present, the appearance of the tumour, it was thought, required one less mutational stage. In Knudson's view, two mutational events were necessary for the appearance of a retinoblastoma, that is to say cancer of the retina in a subject without family precedents of this kind.[3] In short, the accumulation of mutations in the cells of the organism provoked the oncogenesis.

Genetic mutations in man

A man is a cellular city made up in average of over sixty thousand milliard (sixty trillions) of cells. During the course of an average human life, and when a gene-mutating agent is not at work, we have: 10^{17} cell divisions; the incorporation of 6.10^{26} nucleotides; during the course of replication we have errors of 10^{-9} to 10^{-11} caused by incorporated nucleotides; and thus during the10^{16} mitoses that take place on average during the life of a human being each genes is subjected to 10^{8} to 10^{10} mutations. Thus it is that the risk of genetic mutations and the risk of contracting cancer increase with age (Fig.1).

1.2. In what ways can a cancer be hereditary (Fig. 2)*?*

Thus we can speak about pathologies of the DNA which create a predisposition to cancer in the following way. At a family level through: monogenic Mendelian transmission; polygenic transmission; and synergic interaction between the genes and the environment of lifestyle. At an individual level through: specific polymorphisms of the gene that lead to the appearance of one or another form of cancer in the subject who is the carrier, and a large number of subsequent mutations that activate a pro-oncogene or deactivate a regulator or suppressor gene. Such an accelerated accumulation of mutations of the DNA lead to the premature creation of a critical number of genetic alterations in a cell of the organism that will generate a tumour.

2. Predisposition to latent genetic diseases

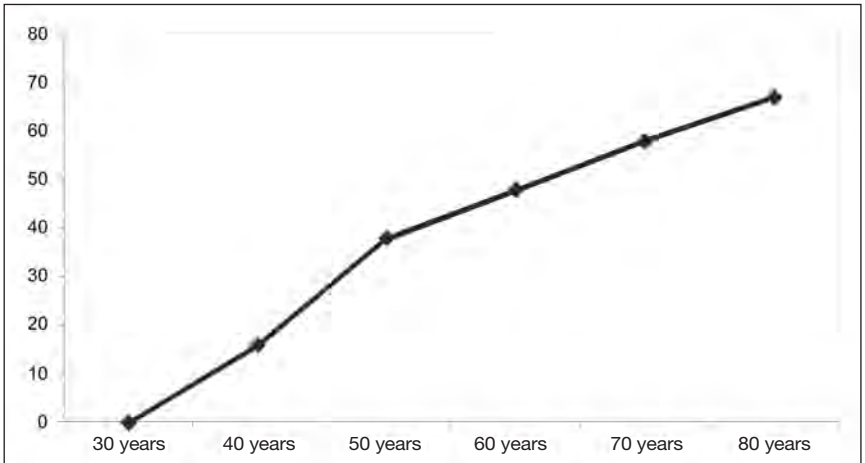
Hereditary genetic illnesses appear a number of years after birth. As in the case of tumours, latent genetic diseases are brought about by genetic mutations. The mutated gene: no longer codifies a protein which remains, however, essential to the organism; or codifies a toxic protein which is injurious to the organism. The following table gives some examples of latent genetic diseases:

II. THE MOLECULAR MECHANISMS OF PREDISPOSITION TO CANCER

Pathologies of DNA are caused by: chance replacements of the nucleotides at the moment of replication; exposure to ionising radiations; cancerogenous chemical substances; viruses.

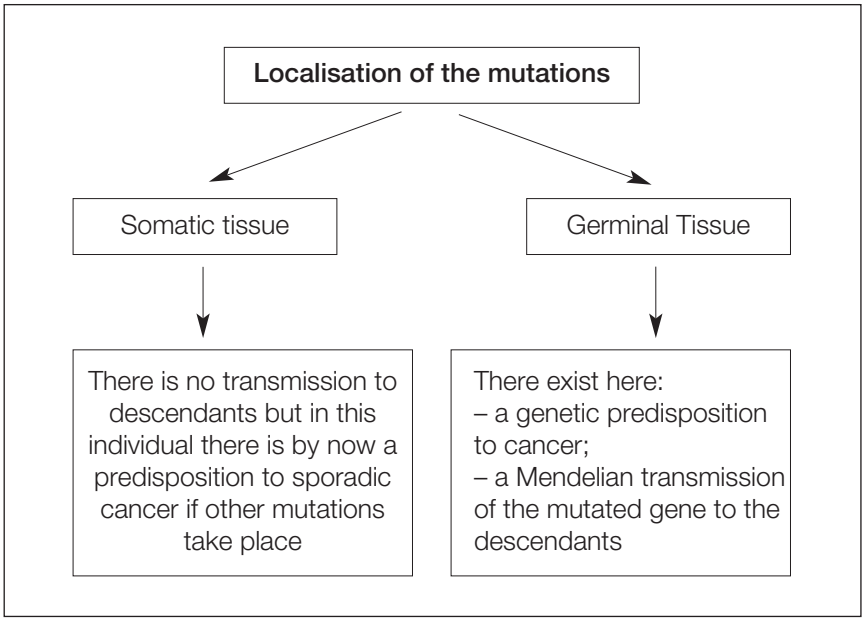
Thus the three fundamental stages of cancerogenesis are as follows: initiation; promotion; progression. In the setting in motion of the process of cancerogenesis various types of regulator genes are activated or deactivated.

Fig. 1



Clauss *et al*:[4] 38% at the age of fifty; 67% at the age of eighty.

Fig. 2



Tab. 1

Syndrome	Illness	Gene	Localisation	Years
Kennedy's disease	Amyotrophy	CAG	X en q11-12	30
Joseph Machado's disease	Cerebral ataxia	SCA2	6p	70
Friedreich's ataxia	Neurological	GAA	9q13	<15
Stumpell-Lorrain's disease	Spastic paraplegia	SPG5	8q; 15q; 10q	35
Addison's disease	Adrenoleuco-distrophy	ALD	Xq28	40
Huntington's disease	Neurodegenerative	CAG	4p16.3	45
Alzheimer's disease	Neurodegenerative	APP	Chromo. 21	60
Amyotrophic lateral sclerosis	Neurodegenerative	SOD1	22q12.2	50
Gilles Tourette's syndrome	Disabling	DRD4	11p15.5	<21
Strargardt's disease	Macular dystrophy	ABCR	1p22.1	<12
Leber's optic atrophy	Optic neuritis	A340H	Plastosomes	<40
Type 2 neurofibromatosis	Nerve tumours	NF2	22q12	<30
Renal polycystosis	Renal insufficiency	PKD1	16P13.3	<50
Cystinosis	Metabolic illness	CTNS	17p13	<12
Morquio's disease	Metabolic illness	MPS IVA	16Q24-3	>10
Gaucher's disease	Metabolic illness	N370S	1q21	<60
Wilson's disease	Metabolic illness	WND	13q14	X>5
Genetic haemochromatosis	Metabolic illness	HFE	6p21.3	<60

1. The proto-oncogenes that stimulate growth

A proto-oncogene is a gene whose action controls cell proliferation in a positive way. The mutation of one of the alleles is dominant. After mutation, the proto-oncogenes become oncogenes and acquire functions and further stimulate cell proliferation. The following are examples of proto-oncogenes: small plates growth factors; growth factors; regulators of the cell cycle (cyclin D). The mechanisms of the activation of the proto-oncogenes are: specific mutations; gene amplification; chromosome translocation; viral insertion.

2. The genes that inhibit growth: tumour suppressing genes (TS) or anti-oncogenes

An anti-oncogene is a gene involved in the regulation of cell growth. The products of the suppressor gene inhibit cell proliferation.[5] Such recessive mutations induce a loss of function and foster cell proliferation and thus tumour development. The following are examples of genes that suppress tumours: the BRCA1 gene (which induces the formation of breast cancer); the RB gene (which causes cancer of the retina); the p53 gene (which fosters the processes of apoptosis).

3. The genes involved in the repairing of damaged DNA

This class of genes watches over the state of the DNA during replication. If an error is made, the complex stops the replication and induces a correction.

4. The genes that regulate programmed cell death (apoptosis)

The products of the Bcl-2 gene inhibit apoptosis, that is to say programmed cell death. Of the great systems of action against the human organism we may list, for example: cell proliferation and programmed cell death, apoptosis (which is different from necrosis, the violent death of a cell). These two systems have to be in equilibrium. If the action of apoptosis is greater than that of cell proliferation, there is an involution in the organism. In contrary fashion, if the action of cell proliferation is predominant, there is an evolution towards oncogenesis. The balance of these two biological mechanisms fosters the development of life.

5. The genes of the metabolism of carcinogenous endogenes and exogenes

The genetic predisposition to lung cancer, caused by smoking, for example, is connected with the genetic polymorphisms or to allelic forms of the enzyme systems involved in the response to toxic agents or mutagens. If a person is predisposed to this type of lung cancer, if he or she does not smoke or live with a person who smokes he or she will not run the risk of developing this illness.

But our understanding of the origin of tumours depends on the state of our contemporary knowledge: the paths of the transduction of the signals that induce cell proliferation; the proteins that control or limit the cycle of cell division; the mechanisms that regulate apoptosis.

III EXAMPLES OF PATHOLOGIES OF DNA INVOLVING GENETIC PREDISPOSITION

The molecular mechanisms of genetic disease vary from one kind of pathology to another. But their common denominator is thought to be a malady of the DNA, a genetic mutation.

1. Retinoblastoma

The retinoblastoma is a tumour of the retina that afflicts almost one in every twenty thousand babies. It is linked to the non-activation of two alleles of the RB1 proto-oncogene at the twenty-seventh exone on180000pb for 4700b RNAm. The proto-oncogene RB1 in involved in the control of cellular division at the level of the transition between the G1 and S phases. This illness generally appears as a dominant phenotype although the mutation is recessive.[6]

2. Breast cancer

According to the *INSERM-FNCLCC, Ann. Genet. 1999*, collective experience one can speak about a risk of hereditary genetic breast cancer in the case of: breast cancer at an early age (on average at the age of forty three for the family forms); family forms: at least two or three first degree cases in a family branch; a bilateral tumour lesion; ovarian cancer associated with breast cancer; breast cancer of a medullar kind. The genes that have been identified that are thought to provoke breast cancer when there is a mutation are:[7] BRCA1, BRCA2, CHEK2 and TP53.

The BRCA1 gene is a large gene located on chromosome 17q and contains twenty-two exones that code 1.683 aminate acids. Over five hundred mutations or sequence variations have already been described and most of the time for each family a mutation seems to be unique. Isolated in 1995, the BRCA2 gene is located on chromosome 13q12-13 and

has no homology with the BRCA1 gene. Over one hundred different mutations have been named, with very few mutations shared by families. Women who are carriers of a BRCA mutation have: a 40% to 85% risk of developing breast cancer before the age of seventy (this risk being 10% in the population as a whole); and a risk of 10% to 63% of developing ovarian cancer before the age of seventy (this risk being 1% in the population as a whole).

3. Lynch's syndrome

Lynch's syndrome is a hereditary carcinoma of the colon or HNPCC. HNPCC (*hereditary non-polyposis colon cancer*) is caused by the mutation/deletion of one or more genes (a process given the general term of 'mismatch repair') that repair the errors of the replication of DNA.8 In the Western world, one person in every two hundred is affected by a mutation of the HNPCC gene. This type of colon cancer is a hereditary pathology of a dominant autosomic type. Carriers of it run a major risk of developing cancer (colon cancer, endometrial cancer, ovarian cancer, urethra cancer, gastric cancer, intestinal cancer) before the age of fifty. The reparation genes of the DNA, once they have mutated, provoke this kind of cancer and they are: MSH2, MLH1, PMS1 and PMS2. But why is the loss of function dominant from a cancerogenous point of view? A heterozygote cell for the MSH2 gene is always able to repair errors. From this point of view, the loss of function of the MSH2 gene is recessive. It is not the heterozygote cell that provokes the tumour but the mutant homozygote!

4. Huntington's corea

This is a hereditary neurodegenerative affliction of an autosomic-dominant kind. A child who has a parent who is a carrier of the mutated gene has a 50% risk of inheriting this gene. Huntington's corea provokes the destruction of the central grey nuclei – the caudate nucleus, the putamen. An unequal crossing over provokes the formation of triplets of over thirty-five CAG nucleotides at the level of the short arm of chromosome IV (4p16.3). The CAG triplet, repeated at the end of the gene, codifies for glutamin.[9] The gene then produces the 'Huntingtonian' protein which is thought to foster the development of the illness.[10] For some researchers the protein p53 plays an essential role as a suppressor of tumour because it is a transcription factor at the level of the nuclear DNA. The protein p53 is, however, equally expressed in the neurons of the brain. In these cells, which divide very little its suppression leads to neuronal death. In the year 2000 it was demonstrated that protein p53 could link itself to the mutated Huntingtonian protein (mHtt), the protein responsible for Huntington's disease. At the beginning of 2005 Bae *et al.* (2005) demonstrated the influence of protein p53 on the process of the development of Huntingdon's disease.[11] In their view, the p53 is equally increased in the brains of mice who overexpose the mutated Htt and in the cortex and the striatum of patients afflicted with this illness. At the present time the diagnosis of Huntington's corea is based upon research directed towards the expansion of the AG triplet through PCR(polymerase chain reaction), followed by the separation of the fragments (on the d'agarosa gel or acrylamide) and sequencing.

5. Alzheimer's disease

Alzheimer's disease is a complex genetic illness. 10% of cases are transmitted in a dominant autosomic way with a complete penetration. The first signs of the disease appear at their earliest between the age of fifty-five and sixty in these families.[12] Alzheimer's disease is above all else a disease that afflicts the memory. All the mnesic processes are afflicted (codification, storage, recall, consolidation). The genes involves in this illness are: APP, PS1, PS2, ApoE and $\epsilon 4$.

PROSPECTS AND CONCLUSIONS

At the present time over six thousand kinds of hereditary genetic illnesses have been identified. The ideal would appear to be that of having diagnostic tests for

all these illnesses so as to identify them in time, to prevent them and to be able to analyse their carriers. But which are the illnesses for which genetics today proposes identification tests and prospects of treatment? There are diagnostic genetic tests for some dominant and recessive monogenic illnesses.

Some examples of latent genetic illnesses for which there are or could be diagnostic test kits (Tab. 2).

A chronogram of activity: identify the genes involved in predisposition to tumours and latent illnesses; encourage companies to develop diagnostic kits: micro-array, micro-pulce or primers systems which are highly specific for molecular tests; create well trained multidisciplinary teams – geneticists, medical doctors, psychologists, social workers; promote regional and national centres of excellence for reliable diagnoses of genetic illnesses; make these tests, pre- and post-test counselling and the medical and psychological analysis of patients free; promote research into the therapeutic prospects for these genetic illnesses; genetic tests for the identification of latent tumours and illness with a view to more advanced forms of treatment that must always respect the human being, his or her rights, his or her fundamental freedoms, his or her private life and his or her human dignity.

Today, genetic predisposition to tumours and latent diseases constitutes for humanity a real drama that is linked to the risks of genetic transmissions and the merciless mechanisms of oncogenesis.

Signs of hope: a day will come when, thanks to the advances of science, all genetic tumours and illnesses, which are very much feared, will be eradicated. On that day man will be reconciled with mother nature and his life will once again shine harmoniously in the rediscovered Garden of Eden.

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Tab. 2

Predisposition		OMIM N°	Frequency 2	Principal tumour sites	Chromosome localisation
Gene involved (3)	**HNPCC** (Lynch's syndrome)	114400	1/500	Colon, stomach endometrium,	2p, 3p, 2q, 7p
MSH2, MLH1PMS1, PMS2	**Hereditary breast cancer**	113705	1/500	Breats, ovary prostate, colon	17q, 13q…
BRCA1, BRCA2..	**Neuro-fibromatosis type 1** (Recklinghausen)	162200	1/3 500	Nervous system, multiple sites	17q
NF1	**Adenomatose polyposis** (Gardner's syndrome)	175100	1/10 000	colon and rectum, duodenal	5q
APC	**Hereditary melanoma**	155600	1/10 000	Skin	9p, 1p
MTS1… sclerosis	**Bourneville's tuberous**	191100	1/10 000	Nervous system, kidneys	16p…
TSC2	**Li-Fraumeni's syndrome**	114480	1/30 000	Multiple sites	17p
p53	**Neuro-fibromatosis type 2** (bilateral neurinome)	101000	1/35 000	Nervous system	22q
NF2	**Hereditary retinoblastoma**	180200	1/40 000	Retina, bone	13q

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GIOVANNI NERI

7. Medical Care for Patients and their Families

The subject of medical care for patients with a genetic illness and their families is a difficult one because it refers to an area that has not been well codified. There are guidelines that are sufficiently clear and shared when it comes to the diagnostic path to be followed in relation to a genetic illness, including the administration of genetic tests and other instruments of exploration, just as there also exist guidelines for genetic consultancy. But 'medical care' is a more complex and more overall term which it is in relation to genetic illness is something that is difficult to define. Patients afflicted with a genetic illness cannot (with the exception of rare cases) be 'treated', that is to say they cannot be cured of their affliction, but this does not mean that one cannot provide them with care. We may say, employing an English phrase which it is not easy to translate into Italian – 'we cannot cure, but we can care for'. Providing care generally requires the concerted action of a large number of different specialists, both in the strictly medical sector and in the sector of rehabilitation, the action of whom must be co-ordinated by a special figure of reference. This figure is often, even though not necessarily, a clinical geneticist, who interacts, on the one hand, with his or her colleagues who are specialists who are called upon when occasion arises, and, on the other, with the patient and/or his or her family.

Genetic illnesses have another peculiarity which further complicates the provision of care to a patient, namely that not only the patient but also his or her whole family need to be attended to. Indeed, the presence of a genetic illness in the family is almost seen as a stigma, as a cause of social discrimination. To this is added the fear that the illness will be perpetuated in future generations, and thus the emergence of a sense of guilt and of inadequacy at the level of procreation.

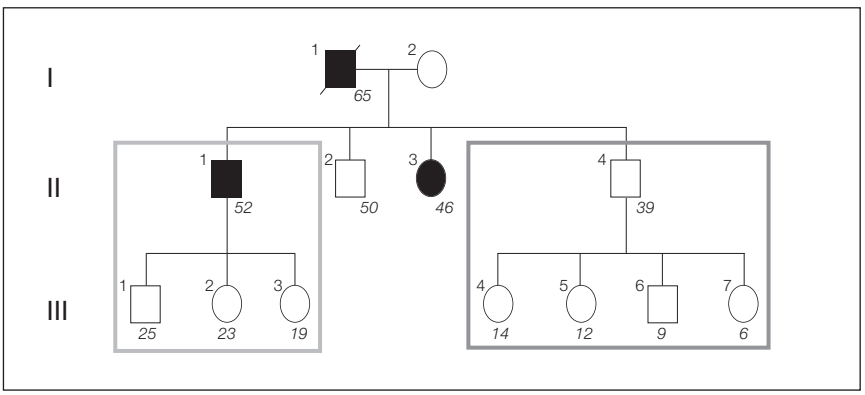
This vast and complex set of issues and questions cannot be tackled by a single health-care worker. It requires a strategy that involves an integrated and multidisciplinary approach that really places the interests of the patient and his or her family at the centre of the actions that are taken. It is difficult to describe such a strategy in abstract terms, not least because, as I observed at the beginning of this paper, an official protocol does not exist which codifies such a strategy with precise canons. Thus it seems to me that one best describe such a strategy with reference to certain practical examples taken from daily experience.

The first involves a family (Fig. 1) in which a well known hereditary disease such as Huntingdon's disease is transmitted, a condition which fortunately enough is rare but which is also well known about and is amongst the most devastating of all hereditary diseases. This disease takes it names from Dr. George Huntington, a family doctor who practiced in Long Island, who identified it during the second part of the nineteenth century and bequeathed to us a description which is exemplary at the level of clarity, accuracy and conciseness. This disease is also known as Huntington's corea because of its movements characteristic of a corea, that is to say involuntary movements of the extremities of the body like those of a dancer. We are dealing here, therefore, with an affliction which is primarily neuro-muscular in character, which can be of varying levels of gravity, from mere tics, at least at the beginning, to a constant contortion of all the parts of the body, a contortion of the body which experiences a truce only during sleep. Often symptoms of a

Tab. 1 - Huntington's disease

• Late emergence of symptoms
• Involuntary movements, especially of the extremities
• Mental deterioration
• Progressive atrophy of the nuclei forming the basis of the brain

Fig. 1 - Genealogical tree of a family with Huntington's disease. Square symbols: males; round symbols: females. The full symbols refer to individuals who are clinically afflicted by the disease. The numbers above the symbols identify each individual subject. The numbers underneath the symbols refer to age in years.

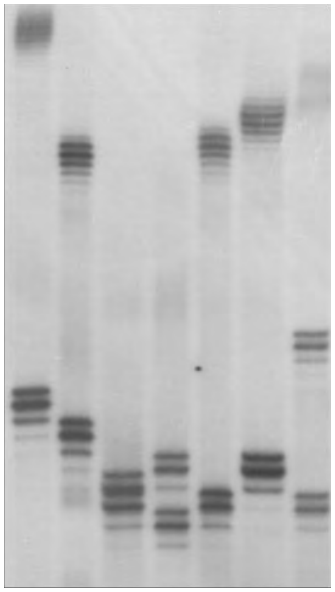


psychiatric character are associated with this malady and they take the form of psychosis or dementia (Tab. I). It is, indeed, not unusual for these poor patients to end their own lives by committing suicide. There is no effective treatment for this terrible malady, which arises late in life, generally not before the age of thirty, and which undergoes a progressive deterioration.

Let us attempt, therefore, to address in a certain order the various and complex problems present in this family, beginning with the group in the left-hand diagram. Here we have a fifty-two year old man afflicted with the disease (II, 1), who received the illness from his father, who committed suicide at the age of sixty-five (I,1), and who at the moment has three children who are apparently healthy (III,1-3). The first problem is to take care of this man, in which the motorial symptoms of the illness are very evident but which are not yet incapacitating. The neurologist is the first specialist to be called into play, even though he or she has available few weapons with which to combat the illness. A few pharmaceuticals directed towards the control of involuntary movements in overall terms are not in fact very effective. Other substances intended to prevent the formation of the cerebral damage characteristic of the illness are still at an experimental stage and are being applied to animals. The possibilities of intervention on the part of a psychiatrist or a psychologist are important, although limited, in order to try to attenuate the tendency to depression which usually accompanies the awareness on the part of the patient that the illness from which he or she suffers is incurable.

The lack of a cure leads us to emphasise above all else prevention and thus to consider the case of the children of the man afflicted by this disease. They are still healthy but given the late appearance of symptoms characteristic of this disease and their young age there are not yet free of the risk of having inherited the gene that causes the illness and thus of being afflicted by it at a later stage of their lives. These young people have two questions that weigh very heavily upon them: whether they will in fact develop the illness and whether they run the risk of transmitting it to their own children. Today the genetics laboratory offers a simple and safe test by which to provide an answer to these questions, a test that shows the presence of the mutant gene even before the appearance of symptoms. It is thus a pre-symptom test (Fig. 2). The simplicity of the application of this test does not, however, imply that the decision to carry it out is simple. Quite the contrary. A test with a positive result is a definitive condemnation and the person who refuses to have it is justified in doing so, even if knowledge about his or her own genetic status would also answer the second question, that is to say whether there exists a risk or otherwise that the disease will be transmitted to his or her children. For these reasons, it is common practice to structure the process involving the decision of whether to carry out the genetic test or not into a series of stages of reflection with the help of a psychologist, stages which never force the person involved to learn the results of the test, even when this test has already been carried out.

Fig. 2 - An example of the genetic-molecular test on samples of DNA for Huntington's disease. Levels 3, 4, and 7 refer to normal individuals. Levels 1, 2, 5 and 6 refer to patients with Huntington's disease.



Similar problems can be encountered in the nuclear family in the right-hand diagram, where the illness is not present. The thirty-nine year old father (II, 4) could still be at a pre-symptom stage. Amongst other things, in his case the decision to undergo a genetic test and to know its result would also have indirect consequences for his children who, implicitly, would be recognised as being potential carriers of the mutation or otherwise. This is a further reason for reflecting carefully on the wisdom of undergoing the test. With respect to the children of this man (III, 4-7), given their young age, their being subjected to this test is something that can be excluded.

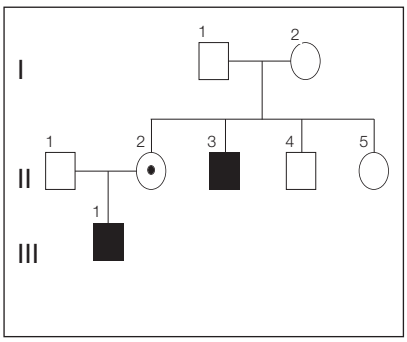
In conclusion, we are face to face with an extremely complex set of issues and questions that require the action of a trained team made up of at least four specialists – the molecular biologist who administers the test, the neurologist, the psychologist/psychiatrist, and the genetic consultant – each one of whom works according to his or her specific role but whose action must be carefully co-ordinated so that discordant or contradictory (or potentially such) messages do not reach the patient. To be really effective this process must be prolonged over time. In other words, the family must be cared for in an overall sense, and each member of the family must be followed according to his or her special needs and interests, which do not, in fact, necessarily coincide with those of the other members of the family.

A second example, which is useful in illustrating other questions and issues connected with caring for families with a genetic illness, is that involving fragile chromosome X syndrome, a hereditary condition that causes mental retardation, in general of a moderate degree (Tab. II). The mutant gene responsible for this – FRM1 – is localised in the chromosome X and thus the illness prevalently afflicts males, to whom it is transmitted by their mothers who are healthy carriers. Let us consider a

Tab. 2 - Fragile X Sindrome

• Mental retardation
• Hyperactivity
• Attention defect
• Anxious behaviour
• Hyper-reactivity
• Modest physical anomalies

Fig. 3 - Genealogical tree of a family with fragile X. syndrome The full symbols refer to two males with the syndrome. The partially full symbol refers to a healthy carrier.



family (Fig. 3) in which there are two people afflicted by this condition, an uncle (II, 3) and a nephew (III, 1), and a mother who is a healthy carrier (II, 2).

The questions and issues that this family has to address at the social level and the level of care are many in number and complex in character. First of all, there is the problem of diagnosis. Mental retardation, which is the most characteristic sign of the syndrome, in general is not clearly evident before twenty-four to thirty months of age. Before this period of development it is objectively difficult to make a diagnosis of the fragile X syndrome, and unfortunately this is also the case after that age if one does not have a good knowledge of this syndrome. All too often we encounter stories of families who go from one centre to another, and at times also abroad, in search of a diagnosis that is not carried out, with great expenditure of physical and mental energies, and at times at great economic cost, and above all with the risk that being unaware of the genetic character of the problem in the meantime other children who are unknowingly also afflicted are brought into this world.

Once again the case should be addressed with an integrated approach. The medical doctor who has the first contact with the child, whether a paediatrician or another kind of specialist, must be able to direct the family to a centre where the genetic test can be carried out that confirms what was suspected at a diagnostic level and which can subsequently follow the afflicted child, entrusting him or her to various kinds of health-care workers, from specialist doctors to rehabilitation technicians, according to the needs involved, and then of course handing him or her over to the school system which includes dedicated support teachers. This accompanying of the family will last for years because the problems and need change with the passing of time. The problem of integration into the school is followed by that of integration into the world of work, or alternatively the obtaining of an invalidity pension. These are difficult pathways which are often troubled by bureaucratic complexities that families are not always able to deal with on their own. And this is not to mention other emergencies, often of a behavioural character, which can arise in people afflicted by this condition and which require special forms of intervention, at times of a pharmacological kind as well.

And then there is the family, all its other members, many of whom can be in a condition of genetic risk. Let us begin with the mother who is a carrier (II,2), a carrier of what in technical jargon is called a pre-mutation. She runs the serious risk of having other children with this disease, a risk that the genetic consultant must be able to quantify exactly and explain clearly, just as he or she must be able to outline the option of having a prenatal text during pregnancy. This opens up a scenario that is full of doubts, uncertainties and moral dilemmas, which for the umpteenth time require that action is taken to support freedom of choice, on the one hand, and the sacredness of human life, on the other. And if this was not enough, this woman may have another problem to face up to, that of a possible early menopause, something that is relatively frequent in women who are carriers of a pre-mutation. She must thus be sent to a specialist who is competent in this field. The younger sister (II, 5), given that she does not yet have children, and in particular children afflicted by this disease, is not necessarily a healthy carrier, but she certainly runs the risk of being one. As such, she has the right to be suitably informed about the possibility of carrying out a test to ascertain if she is a healthy carrier. The healthy brother (II, 4) could be the carrier of a pre-mutation of the FRM1 gene, which in itself does not involve the risk of having children with this disease –if anything only daughters who are healthy carriers – but rather that of developing at a later stage in life a syndrome of a Parkinsonian kind, at times also with dementia.

An illustration of these two emblematic cases demonstrates the complexity of the problems involved, problems of both a health-care and a social kind, which accompany those people who are afflicted by a genetic disease and their family relatives, and brings to the fore the need to address these problems with initiatives that are at one and the same time specific, effective and economically tolerable. This is certainly much easier said than done. The national health service and the service providing social support are an asset of great value for our country but they are also an example of the famous short blanket which ends up by being drawn towards the sectors that have most social voice. As regards the health-care sphere, one need only think here of cancer patients; as regards the social sphere, one need only think here of the elderly. Fortunately, genetic illnesses are rare but this good fortune is transformed into misfortune for those who are afflicted by them because their problems tend to be forgotten or to take second place in relation to more urgent problems and problems which have a higher priority. Fortunately, a great deal of help is provided by the families themselves which, indeed, come together in support associations in order to know more about the genetic illnesses which afflict them,

provide each other with mutual support, promote their cause in relation to political institutions, and advance research.

This does not remove the fact that the question of caring for families with a genetic illness is serious and cannot be ignored. We have come together at this international conference to talk about the human genome, beginning with the definition of health as a 'tension towards harmony', which has its foundation specifically in the human genome. If during the course of the natural history of mankind, or during the course of the life of a single individual, elements of imbalance are introduced into the human genome which cause illness or suffering, thereby impeding or slowing down the achievement of this harmony, then it will be our task and our precise duty to correct this anomaly with the licit means that science and nature herself make available to us. As regards tomorrow, we hope for effective gene therapies. This does not exonerate us from thinking about today and our responsibility to create other forms of intervention which, however much they may be palliative in character and provisional in form, are nonetheless the best that for the present we can and must give to our less fortunate brothers and sisters. This is a task that falls to each one of us individually and to society as a whole.

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AUBREY MILUNSKY

8. Judgement, Error and Negligence in Genetic Aspects of Maternal Fetal Medicine

Janus, the mythical Roman God of Gods, apparently had the ability to look in opposite directions at the same time. The twin abilities of foresight and hindsight would shed miraculous light on the practice of obstetrics, perinatology and clinical genetics in particular. Deprived as we are of such remarkable gifts, we are left to cope with our inherent limitations in achieving sound judgement.

Among the various definitions of judgement, biblical or otherwise, are exhortations and invocations of wisdom, discernment, discretion, knowledge, understanding and good sense. Integral to the logical definition of judgement is the necessary action of the mind that apprehends the relation between at least two objects of thought. Key ingredients necessary to achieve sound judgment include wisdom, knowledge and experience. While the accretion of knowledge is a lifelong challenge, the emergence of wisdom is not inevitable. Sir William Osler captured the essence of the difference:

"Knowledge is proud that he has learned so much:
Wisdom is humble that he knows no more".

Ultimately, a synthesis of knowledge and experience tinctured with sensitivity and insight into the human condition may encourage the emergence of wisdom. Either way, in the practical world in which we live, the clinical practice of medicine, and for this discussion, maternal-fetal medicine and clinical genetics, requires the uniform acquisition and application of these qualities. Graduated senior oversight enables the ready interdigitation of these qualities, hopefully for the betterment of medical care.

Judgement

The practice of obstetrics or perinatology including concerns about fetal genetic health, invokes a cascade of requirements for effective decision-making. The invariable focus in clinical practice focuses on factual knowledge and clinical expertise.

A remarkable chasm exists between the necessary practical elements of decision-making, especially in the face of recognized hazards, and the known antecedents for sound judgement. Universally we have done poorly in educating our physicians about these necessary antecedents. We have failed to provide them with clearly enunciated guidance about those factors that influence discretionary judgement and decision-making. Can any physician remember formal instruction on the quintessentials of clinical judgement or on the genesis and avoidance of errors? Clinicians faced with decision-making under emergency circumstances that include labor and delivery or the management of potential or real fetal abnormality need to have been schooled about the factors, beyond knowledge and experience, which potentially influence thought processes and which may affect critical decision- making.

Perceptions of risk vary between individuals. A 10% risk of an adverse event is highly worrisome to some, but regarded as an insignificant problem by others. Not infrequently a physician and his/her patient may have an entirely different view of the risks to be faced. Personality type can also have important influences on the perception of risk and probability. We already know about individuals who are significant risk-takers and indeed there are genes that appear to show certain individuals as novelty seekers (or high risk-takers). These very same individuals may reach conclusions of certainty in contrast to their more conservative colleagues who might remain uncertain. The same breed of risk-takers is likely to exhibit overconfidence when a lack of confidence might be more appropriate. Individuals (including some physicians) with these personality traits are less likely to quickly recognize increasing danger (or hazard to the patient or fetus) and to be less likely to call for help or consultation. Estimates of risks are fallible and the degree of fallibility may be remarkable. Unfortunately, poor estimates of risk may be held with great confidence more especially by individuals who have limitations in the recognition of their own abilities. Moreover, errors of judgement may be a consequence of poor reasoning. Failure to frame the question precisely or recognize the specific hazard in a timely manner may often lie at the root of the ensuing catastrophe. Consider the following saga which culminated in litigation.

"Mrs. L aged 22 had a history of bleeding intermittently through her pregnancy. While in labor in hospital she had a sudden heavy vaginal bleed, became hypotensive and anemic and the electronic fetal monitor registered a fetal heart rate that dropped to between 50 and 60 beats per minute. Epidural anesthesia was administered (inadvisable in the face of an emergency) and cesarean section was performed. At birth, HL had no heart beat and no respiration, was blue and floppy, had metabolic acidosis, anemia, a low platelet count (meriting platelet transfusion), and a very high nucleated

red blood cell count. Emergency resuscitation measures were taken within one minute of birth. Kidney failure (anuria) became evident and ultrasound study revealed acute tubular and cortical necrosis and HL was placed on peritoneal dialysis. In addition, HL suffered pulmonary edema and hemorrhage, and developed respiratory failure. HL's status at birth was pathognomonic of severe and prolonged hypoxia beginning at least during labor and delivery. Contrary to expectations, the kidneys did not recover, peritoneal dialysis continued, and it became clear that he would require kidney transplantation to survive. At ten months of age imaging studies of his abdomen revealed a large tumor (neuroblastoma) of his adrenal gland adjacent to one kidney. Both tumor and adjacent kidney were surgically excised. The remaining failing kidney was the cause of developing high blood pressure eventually remedied by removal and kidney transplantation from his donor father. The parents claim that their son's kidneys were ruined by hypoxia during labor and delivery were countered by the defense position that given his perfectly normal intellectual development and absence of neurological involvement, oxygen lack could not have been the cause. With the wisdom of hindsight we now know that neuroblastoma is an embryonal tumor which must have already been present at birth and secreting adrenalin-like products in excess due to the stimulation of hypoxia and further abetted by the administration of adrenalin-like drugs used in HL's resuscitation. All of these agents synergistically must have seriously impaired blood supply to the kidneys and effected irreversible damage."

In dealing with the complexities of the human body, critical and unexpected malfunctions may occur. A tendency to overestimate the probability of conjunctive events and to underestimate the probability of disjunctive events will invariably invite trouble. There is a general tendency to underestimate the probabilities of failure in complex systems. Worse still, is that some people (including physicians) view themselves as personally immune to certain risks believing "it won't happen to me". There is also a natural tendency for people to see what they expect to see rather than what's readily apparent. This is an inherent problem and an important source of medical error. Many other factors not discussed here include the influence of mood, fatigue, depressive or optimistic personality, sensitivity, among other considerations, on decision-making. What is clear however is the need to educate our medical students and practicing physicians about otherwise unrecognized antecedent factors that unwittingly influence their decision-making that may ultimately prove harmful to their patients.

Decisions by Patients

Patients too, faced with serious health decisions may reach unexpected conclusions. Experienced clinical geneticists have seen couples who despite high risks have, for example, had three children with cystic fibrosis or the Fragile X syndrome. Clinical geneticists in the Western world adhere to a consensus of non-coercive, nondirective genetic counseling. Hence, there are no "wrong decisions", since patient autonomy and physician beneficence emphasize key and universal ethical principles. Notwithstanding adherence to patient autonomy, there is clear recognition of factors that also influence decisions made by patients in the face of serious risk. Key among those factors are educational level and knowledge, religious affiliation, personality traits (risk takers vs. risk averse individuals), understanding of probability, perception of an expected burden of illness/defect, the degree of anxiety, and the experience of a previously affected child.

Given the many factors that impact decision-making by future parents with reference to serious or fatal genetic disorders, strict adherence to non-paternalistic genetic counseling, free of bias or prejudice, remains a standard in the Western world.

Error and negligence

The American Institute of Medicine in their publication "*To err is human: Building a safer health system"* reported that as many as 98,000 people die annually in the United States as a result of medical errors. One response, besides incredulity, was to blame any attributable negligence to simple human error operating in an intrinsically hazardous system. The point that an operating system was devised by man seems to have received insufficient attention. James Reason posited the view that since errors were largely unintentional, it was difficult to control what people did not intend to do. This argument fails to recognize the importance of anticipatory planning and a clear understanding of opportunities that exist for the avoidance of unintentional but not necessarily surprising errors. Many errors subsequently deemed negligent, could have been anticipated and avoided or prevented.

In maternal fetal medicine, there is an overabundance of medical malpractice litigation in the United States and increasingly elsewhere. An extensive array of factors operates in this milieu and will not be fully covered here. Initiating factors leading to litigation are the patient's urge to hold someone culpable for the adverse event, to blame, to punish, to seek compensation or to warn others to protect themselves. Frequently, the patient or family exhibits anger about the events that led up to the adverse result and the poor communication skills and lack of physician rapport adds fuel to the fire. Sometimes

the patient's perception of events is unrealistic, but frequently there has been poor communication more especially about known risks, doubt and uncertainty. In the clinical genetics context in maternal fetal medicine, the physician invites legal intervention when there is a failure to make a diagnosis that results in death or disability, when there is a failure of communication, or there is carelessness in the execution of expected treatment or management. A brief discussion of some of these failures follows.

Failure to make a diagnosis

Failure to make an accurate diagnosis is not in and of itself negligence. If however subsequent harm or damage ensues to the individual, family or offspring, a conclusion of negligence may be reached. Negligence however cannot necessarily be inferred from an adverse outcome. Moreover, physicians are not held to a standard of perfection. Rather, common law in most Western countries holds physicians to a standard of expected care. That standard reflects what the average and prudent physician would reasonably do under similar circumstances. Beyond the reasonable, prudent and average standard, physicians are also expected to encompass advances that are of such importance and which cannot be ignored. The famous 1932 T. J. Hooper case in the United States set the stage for the necessary uniform acceptance of obvious beneficial advances. In that case, a tugboat operator failed to use a radio receiver which was widely available and would have provided early warning of a storm before any loss was suffered. In that case, the famous Judge Learned Hand opined that *"there are precautions so imperative that even their universal disregard will not excuse their omission"*. Subsequent court decisions have enshrined that view together with the recognition that physicians have "a duty to stay abreast". Further precedent emerged from a 1996 decision from the Supreme Court of Wisconsin which stated that *"A reasonably competent practitioner is one who keeps up with advances in medical knowledge"* and the Court accordingly apprised the jury of such an obligation.

One example of diagnostic failure resulting in litigation is a family who ultimately had three children with the Fragile X syndrome. Failure to diagnose this disorder in their first son for some six years deprived the parents of an opportunity to avoid having further children affected with this mental retardation syndrome. The legal doctrine that advances the claimant's view is entitled *"Loss of Chance"* and which in essence deprives individuals and families of opportunities to avoid or prevent serious illness, disability or death. In a similar vein, but with further implications, the following litigation ensued.

The daughter of a father who developed familial adenomatous polyposis (colon cancer) sued her family physician for not advising her of the 50% risks for developing the same genetic form of colon cancer and the necessary required surveillance. She did indeed become victim to the same cancer.

This case introduced extended liability in the context of genetic diagnosis and counseling. Physicians are seen to have additional responsibilities and duties at least so far as warning next of kin about life-threatening risks. An extension of these duties may emerge with continuing dramatic advances in human genetics. Responsibilities may devolve upon geneticists and other physicians to re-contact patients for whom new diagnostic, carrier and prenatal tests have developed.

Technological developments including those used in the management of pregnancy have provided enormous benefit to many patients. However, significant failures in procedural execution and imaging analysis continue to occur.

During a routine pregnancy, a level II ultrasound at about 16 weeks of pregnancy was reported as entirely normal. At birth, the child was born without arms or legs.

The clergy and geneticists are frequently asked in these circumstances, especially by many who practice their faith, where was God?

Genetic Counseling and Communication Failures

Proper communication concerning genetic disorders, risks, tests and treatment, require sophisticated understanding of the human condition besides an in-depth knowledge of clinical genetics. Physicians in many specialties unwittingly provide genetic counseling only to find later (often to their chagrin and the patient's dismay) that multiple issues which should have been addressed either escaped their attention entirely or about which they were ignorant. At least in the United States, genetic counseling is best provided by American Board of Medical Genetics certified clinical geneticists and genetic counselors. Examples of failures abound.

An obstetrician delivered a baby who was diagnosed as having polycystic kidney disease. He communicated to the patient that there would be a 1 in a million likelihood that this would happen again and that she could go ahead and have another child, the affected child having died. She did, and delivered a second affected child, who also died. For this autosomal recessive disorder, the risk of recurrence was 25%!

Multiple cases have occurred where the physician has failed to pay attention to the family's ethnicity. Such failures resulted in no carrier tests being offered for disorders specific to the ethnic group, including sickle cell disease (blacks), Tay-Sachs disease (Ashkenazi Jews), and ,-thalassemia (Italians and other Mediterranean peoples). Failure to detect that both parents are carriers (with 25% risks of having affected offspring) did indeed result in the birth of children with each of these specific disorders.

Communication failures may also occur between physicians.

A blind woman presented for routine obstetric care. Her eyes had been surgically removed when she was a toddler. She had been adopted in early childhood and had no idea about the reason for her enucleation. Her obstetrician

failed to even inquire about the cause of her blindness and she subsequently gave birth to a child who at the age of nine months was diagnosed with bilateral retinoblastoma (genetic cancer of the eye). There was in fact a 50% risk that this mother had for bearing a child with retinoblastoma. That child's eyes were also eventually enucleated.

Physicians stymied by a patient's presentation and lacking a diagnosis are expected to consult or refer (aside from the expectation of sensitivity in inquiring about the cause of her blindness), more especially since about 9,000 genetic disorders and traits have been catalogued. Failure to make a diagnosis of a rare genetic disorder is not the issue. Rather, it is the failure to consult or refer.

Given the modern complexities in the practice of medicine, it is not uncommon for a patient to be cared for by at least two physicians. It would seem obvious that such physicians would be in communication with one another while caring for their patient in-common.

A patient with epilepsy presented for routine obstetrical care. Her anticonvulsant medication was valproic acid. This medication is well known to cause valproic embryopathy and was being administered by her neurologist. Her obstetrician, without communication with her neurologist, assumed that appropriate changes had been made in her treatment regimen. No such communication ever occurred and this mother delivered a child with severe spina bifida, hydrocephalus and mental retardation due to the medication.

Management Failures

Not infrequently, the smallest details that require attention are missed with catastrophic consequences. While errors in the "system" are often held culpable, it is individual physician failures due to a combination of dependence upon others, fatigue, being harried, multi-tasking, ignorance, arrogance, and not caring.

A woman underwent amniocentesis for prenatal genetic studies because of a 25% risk of having a child with cystic fibrosis. The requisition form, filled out by the ultrasound technologist, failed to order the specific cystic fibrosis DNA test which, as a consequence, was not done. The child was born with severe cystic fibrosis. A similar case reflected the failure to specifically arrange and order a test for X-linked myotubular myopathy following amniocentesis for prenatal studies and the child was born with this lethal disorder.

Uncertainty pervades virtually every facet of life with which we have to contend. The patient's perception of reality and risk may reflect unrealistic expectations without knowledge of the standard calculus of probability or the laws of probability theory. Doubt and uncertainty may leave their indelible mark on our every day lives, but opportunities to wisely interpret the facts as known and to share information at the boundaries of ignorance, cannot be missed. Certainly anticipatory planning and forethought could markedly decrease the frequency of unintended error, thereby increasing patient safety. Advances in human genetics present new approaches to benefit mankind. We need to ensure that these opportunities occur ethically and with necessary wisdom.

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CHRISTINE M. ENG

9. The Development of Dignostic Tests for Genetic Diseases

Introduction

Genetic testing is defined as a laboratory analysis designed to detect abnormalities that cause or are likely to cause a specific disorder. The analysis can be designed to detect abnormalities at the DNA, RNA, chromosomal, or biochemical level.

There are many types of genetic testing. These include diagnostic or confirmatory clinical testing in which a presumptive diagnosis of a genetic syndrome is made based on clinical signs and symptoms and testing is recommended to confirm the diagnosis. Presymptomatic genetic testing in which there is generally a known family history of a late-onset genetic disorder such as Huntington's disease and testing is requested to determine whether an asymptomatic individual is at-risk to develop the disorder. Presymptomatic genetic testing can also be applied to cancer genetic testing, in which a familial increased risk of cancer can be associated with the presence of a BRCA1 or BRCA 2 gene mutation. In general, presymptomatic genetic testing of minors is not performed unless a treatment intervention or screening protocol should be instituted at an early age in individuals who have been found to be at risk. Pharmacogenomics, or a genetic test to predict a response to a specific therapy is an emerging tool to optimize and individualize a person's medical treatment. Carrier testing to determine whether an individual has inherited one copy of a genetic change can be requested either on the basis of family history of a known genetic disorder or ethnic predilection for certain genetic disorders such as Tay Sachs disease in the Ashkenazi Jewish population, sickle cell anemia in individuals of African descent or beta-thalassemia in individuals of Mediteraanean descent. Carrier testing is generally performed to determine a couples' reproductive risk for having a child with a specific disorder. Prenatal genetic testing is sought when the fetus in a current pregnancy is recognized to be at increased risk for a genetic disorder, above that of the general population. Preimplantation genetic diagnosis is performed following in vitro fertilization to diagnose a genetic disease in a preimplantion embryo. Newborn screening is performed usually at the government level to detect specific genetic diseases for which early recognition and institution of treatment are key to outcome. Examples include disorders of metabolism such as phenylketonuria and galactosemia.

Advances in all aspects of genetics has lead to a rapid increase in the number of genetic disorders for which testing is possible as well as the number of laboratories that perform testing. Testing can be DNA bases, phenotype based, or chromosome based.

Regualtion of genetic testing is provided at many levels. First, government agencies may dictate which genetic tests may be available. The US FDA monitors the development of commercially available kits for performing genetic testing. Insurance payers also provide a mechanism for review of clinically indicated genetic tests. Professional practice societies study the development of new tests and offer guidance to practioners on the proper settings to offer testing. Patient preferences for genetic testing are also important as all patients must understand the risks and benefits of the testing before proceeding. Informed consent is usually required for genetic testing.

Why is it important for patients to have a definitive diagnosis obtained through genetic testing? The information forms the basis for inheritance, recurrence risk, and prognosis. For many patients, it takes many years and multiple tests to arrive at a diagnosis. The final arrival at a specific diagnosis thus allieviates uncertainty and the risk of undergoing many rounds of diagnostic tests, both invasive and non-invasive. And finally, a specific – in contrast to a non-specific diagnosis – may help in securing health and school services. For example, confirming a diagnosis of Prader-Willi syndrome may assist families in receiving necessary services such as educational intervention, diet and nutritional counseling.

Various molecular methods can detect mutations ranging from a single base change in a gene sequence, to megabase (Mb) rearrangements of genomic DNA. The level of genomic resolution of molecular methods and classical cytogenetics represent two ends of the spectrum. More recently, hybrid molecular cytogenetic methods have provided powerful tools to bridge the gap. This presentation provides an overview of current and evolving DNA-based analytical methods that are applicable to all types of genetic testing, with particular emphasis on array-based comparative genomic hybridization (array-CGH) to detect

unbalanced gains or losses of genomic regions that cause clinically recognized genetic disorders.

Overview of current DNA testing methods

Representative methods currently used in molecular diagnostic laboratories are listed in Table 1. Known point mutations can be detected using various genotyping methods based on PCR amplification followed by resolution of wild type and mutant alleles. Gene mutations that are not known *a priori* can be detected by mutation scanning methods such as heteroduplex analysis. The gold standard for identifying point mutations is considered to be DNA sequencing. Large DNA rearrangements can be detected with classic Southern analysis and pulse-field gel electrophoresis, respectively. PCR-dependent methods are also available for gene dosage analysis.

The Convergence of Molecular and Cytogenetic Diagnostics

Genomic alterations can be resolved at different levels using molecular, cytogenetic, and molecular cytogenetic methods as depicted in this figure. On one end, DNA sequencing resolves single base changes in regions approaching 1,000 bases per read. At the other end, G-band karyotyping detects chromosomal rearrangements at the ~4 megabase level. Intermediate rearrangements are detectable by fluorescence in situ hybridization (FISH) with DNA probes ranging from ~40 to 250kb [4]. However, FISH has limited capacity to screen large genomic regions simultaneously.

Lower left panel shows normal results from Chromosomal Microarray Analysis performed using dye reversal in patient and control genomic DNA which can be thought of as multiple fish tests performed simultaneously.

Multiplex analysis was greatly facilitated by comparative genomic hybridization (CGH) on metaphase chromosomes, which was initially used to detect chromosomal imbalances in cancers [10]. Subsequently, CGH analysis was applied to DNA clones arrayed on slides rather than metaphase spreads (array-CGH).

Patient and normal genomic DNA are labeled with different fluorescent dyes and co-hybridized onto DNA microarrays, and the dye fluorescence ratios indicate relative gain or loss of specific clones [11, 12].

Array-CGH using microarrays containing large-insert genomic clones such as BAC, PAC, and cosmid clones are well suited for the detection of single-copy alterations. The remainder of the material in this presentation deals with BAC microarray, which we also refer to as chromosomal microarray analysis (CMA).

Microarray printing methods have been developed wherein activated DNA is printed on a natural glass surface to produce arrays with uniform spots for precise quantitation [35], while other methods attach DNA to chemically treated slides. CMA was clinically validated at our institution as a high-throughput method for screening copy-number changes in chromosomal regions associated with over 70 specific disorders and 41 subtelomeric regions [38]. The clinical CMA chip is designed to provide high sensitivity to detect well- characterized disorders, while at the same time minimizing detection of variations of uncertain clinical significance. The array also detected some imbalances that were previously undetected by conventional karyotyping.

An example of CMA data from a child with global developmental and speech delay and dysmorphic features who was found by CMA to have a deletion at chromosome 1p36 is shown here.

The majority of clinical cases have been performed using an updated array (Version 5) containing 860 clones which span genomic regions for over 70 known genetic disorders and 41 subtelomeric regions.

To date over 1200 cases have been analyzed in our laboratory

Imbalances were detected in 6.8% (83) out of 1205 unrelated probands with mental impairment, dysmorphism and other abnormalities, most of whom had extensive genetic testing prior to the CMA test. The collective results from over 1200 CMA studies at our institution (probands and additional family members) are continually being stored in an interactive data base, which provides a valuable resource based on actual clinical testing experience.

The complexity of genomic copy number polymorphisms

Genetic variation has been well documented in the human genome. Large–scale variation (LCV) or copy number polymorphisms (CNP) ranging from 100kb to 2 Mb have been characterized using molecular methods. It is possible that these variants in copy number may represent the tip of the iceberg in human genetic variation [44]. When analyzing the genome as a whole, one must be careful in interpreting gchanges, which may be benign variants or truly related to disease.

In clinical cytogenetics, it has been widely assumed that detection of a chromosomal anomaly establishes the cause of a clinical phenotype. This belief over the years has been reinforced by repeated association of a given cytogenetic finding with a distinct phenotype. However, microarray analysis with increased resolution

brings to light atypical findings whose clinical interpretation is complicated by polymorphic copy number variations. It is therefore critical to distinguish between disease-causing and benign genomic copy number variations obtained on CMA, in the same manner that mutations are distinguished from polymorphisms on clinical DNA sequencing analysis. Checking available databases of previously documented genomic copy number variations, as well as follow-up testing on parental samples, can be very helpful approaches towards interpreting the clinical significance of novel findings identified by CMA.

The Application of Array CGH to clinical testing

The clinical use of array CGH could represent a revolutionary transition from molecular diagnostic testing of single gene disorders to molecular screening for genomic disorders in a multiplex manner.

Counseling Issues

A comprehensive genetic counseling program is necessary to provide patients with pre- and post-testing education and support relevant to this novel testing platform. As part of the informed consent process, patients need to be aware of certain caveats which include the following: a) CMA testing is designed to identify unbalanced genomic copy number abnormalities, but not balanced rearrangements or point mutations in disease genes; b) detection rates vary for the disorders tested by CMA, since genomic rearrangements account for varying percentages of total mutations for each disease gene; and c) CMA has the potential to detect novel, uncharacterized abnormalities of unknown clinical significance, which could lead to uncertainty regarding the causative link between the observed variant and the clinical disorder.

As genetic testing technologies such as FISH and DNA sequencing technology were eventually embraced by diagnostic laboratories and health care providers in the late 20th century, CMA has now gained acceptance in the pediatric setting for rapid detection of genomic imbalance. This technology has the potential to offer a higher level of genomic screening over the standard karyotype. The multiplex nature of CMA is comparable to thousands of single-locus FISH tests, which makes it highly efficient and cost effective. It provides an improved level of detection for chromosomal imbalance. As with the introduction of any new technology, we must be cognizant of the potential risks, inform patients fully of these potential risks, and seek to minimize them.

The current availability of this unique testing platform offers clinicians their first opportunity to integrate a powerful tool for genome screening in their medical practice. New syndromes will be identified, and phenotype-genotype correlations with precise chromosomal regions will significantly improve. Specialized arrays will be used for various cancer diagnoses and prognoses in order to monitor effective treatment. A targeted approach may be better suited for more routine studies, whereas a screening approach may be appropriate for diagnostic challenges in the pediatric setting. The major challenges ahead include efforts to educate health care providers and patients regarding the risks and benefits of using this revolutionary technology, and the preparation of medical geneticists and genetic counselors in adequate numbers to help interpret the findings for optimal patient care.

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10. The Genetic Screening of Populations

1. Overview

We are living in a time in which medicine, and particularly genomic medicine, is moving from intense, crisis-driven intervention to predictive medicine. With respect to screening entire populations or specific subgroups for genetic information, it is becoming possible to target interventions to individual patients that may prevent the onset or progression of disease and, generally, improve their health. Population screening is already commonly used to identify persons with certain Mendelian disorders prior to the appearance of symptoms and thus prevent illnesses – one such example is the testing for phenylketonuria in newborns. Selected populations are also being tested for carrier status in prospective parents as an aid in reducing the frequency of certain diseases in subsequent generations. But increasingly genetic information is used to determine individual susceptibility to common disorders such as heart disease, diabetes, and cancer. Such screening is used to identify persons at risk so that primary-prevention efforts (e.g., diet and exercise) or secondary-prevention efforts, such as early detection or pharmacologic intervention, can be initiated. Information gained from the current practice of testing may lead to the ameliorization and the modification of current screening recommendations and – hopefully – to a substantial reduction of the societal healthcare burden, including its financial, emotional and social costs.

2. Current implementations of population genetic screening

Genetic screening involves three elements: 1. Identification of persons likely to be at high risk for a specific disorder; 2. Outreach to populations that have not previously sought medical attention for their condition; 3. Follow-up and intervention to benefit the screened persons. The most universal application of population genetic screening is the example of screening newborns. In many nations around the world, but most comprehensively in the United States, Canada and a number of European countries, all newborn children are tested for a spectrum of rare, debilitating, but treatable diseases. Among these nations, however, and even within nations – in the United States each state has its own testing policy – the particular set of diseases tested varies. A number of different methods for testing exist, and the availability of technologies varies among nations, so that even when there is agreement on which conditions should be tested, there is no guarantee that the same type of test will be applied.

Population screening of adults has been more limited. One example of its application is testing for Tay-Sachs disease, a fatal genetic disorder in children that causes progressive destruction of the central nervous system. Here testing the children would be too late, as there is no known treatment. However, because the disease is recessive, prospective parents can be tested to see if they are carriers of the mutant Hex-A gene. If both would-be parents were carriers, then their offspring would have a one in four chance of having the disease. This disease is too rare in the general population to justify testing all prospective parents, but there are subpopulations in which the frequency is much higher, most notably Jews of Eastern European ancestry. In these populations, screening for Tay-Sachs has become the standard. Other examples of adult screening have been more ambiguous. When mutations causing cystic fibrosis were first identified, plans were made to begin screening for this disease that thickens bodily mucus and can block lungs and damage the liver, but since then over 900 different mutations have been identified and the early promise of screening to help prevent and treat this disorder no longer seems feasible. This is an example of where a negative test would not be very conclusive – an unknown number of additional mutations are presumed to exist and remain to be identified. Hereditary haemachromatosis, where three mutations are known to account for over 80% of cases of this disease that overloads the blood with iron, was then the next hope for screening. Even though a simple treatment exists for this disease – regular blood donation – the fact that people with disease experience a wide range of symptom severity, with most having very mild forms that require no treatment, has led to the assessment that screening should not be applied population-wide, but only in high-risk individual cases as, for example, when a brother or sister is already known to have the disease. A final example is the case of screening for Factor V Leiden. Four to seven percent of people of Northern European ancestry carry at least one copy of the mutated gene. Carriers are much more likely to develop blood clots, which is an especially serious condition and an important consideration when assessing the risks of surgery. Unfortunately, the current treatment for Factor V Leiden disease is to take anti-coagulents, but this treatment itself carries high risks, in particular a risk of 3% per year for haemorrhage – one in five of which are usually fatal. Be-

cause it is not straightforward to assess the risks of the disease versus the risks of the current treatment, it has not been recommended to screen for this disease.

3. The ethics of population genetic screening

Most of the diseases presented so far have been relatively rare in the population. But what about the more common complex diseases, diseases that likely involve multiple genes and gene-environment interactions? A large number of recent genetic studies have begun to identify variants in genes that are associated with modest risks of increasing the chances for common diseases, such as non-insulin dependent diabetes mellitus, Crohn's disease and a number of forms of cancer. In these cases the variants are not rare – screening tests would identify many carriers. The mechanisms by which the mutations cause the diseases, however, are very poorly understood, and treatments tailored to mutation carriers are nearly non-existent. It is often unknown whether environmental triggers are needed in addition to the genetics, or whether mutations at two or more genes need to work together. What is known is that many people with these mutations will never experience the disease and many people without these mutations will get the disease. Yet, there exist many companies that will gladly sell genetic screening tests – providing them to the public with very little counselling or guidance regarding their use and interpretation, even providing tests that can be self-administered at home, with results reported via the internet as though the these should be easy to interpret for the ordinary layman. Such companies, that prey on the fears many humans experience of contracting one of these diseases, are often disreputable, if not reprehensible. Other ethical issues that arise include who can be tested – can the baby in the mother's womb be tested, for example? Or can individuals at high-risk for population threatening diseases be required to be tested, as in forcing prostitutes, homosexuals and intra-venous drug users to be screened for HIV infection? What about secondary information resulting from testing? Here, consider a person who has prepared himself for the possible results of disease A, but wasn't told that it could also identify disease B? Should he be informed that he has disease B even though he hasn't agreed to a test for B? Clearly, standards, both scientific and ethical are essential to population genetic screening, and oversight or regulation will also be needed.

An early set of principles attempting to address some of these issues were developed in 1968 by J.M.G. Wilson and G. Jungner. These principles emphasized the importance of a given condition to public health, the availability of an effective screening test, the availability of treatment to prevent dis-

ease, and cost considerations. The impressive advancements of genetic study and the experience of population screening in the last thirty years, however, necessitates a reformulation and revision of their principles. A recent group of distinguished scientists and ethicists has proposed the following:

3.1 Regarding public health assessment

– The disease or condition which will be tested should be an important public health burden to the target population in terms of illness, disability and death.

– The prevalence of the genetic trait in the target population and the burden of disease attributable to it should be known.

– The natural history of the condition, from susceptibility to latent disease to overt disease, should be adequately understood.

3.2 Regarding evolution of tests and interventions

– Data should be available on the positive and negative predictive values of the tests with respect to a disease or condition in the target population.

– The safety and effectiveness of the tests and accompanying interventions should be well established.

3.3 Regarding policy development and screening implementation

– Consensus regarding the appropriateness of screening and interventions for people with positive and negative test results should be based on scientific evidence.

– Screening should be acceptable by the target population.

– Facilities should be available for adequate surveillance, prevention, treatment, education, counselling and social support.

– Screening should be a continual process, including pilot programs, evaluation of laboratory quality and health services, evaluation of the effect of screening, and provisions for changes on the basis of new evidence.

– The cost effectiveness of screening should be established.

– Screening and interventions should be accessible to the target population.

– There should be safeguards – by law – to ensure that informed consent is obtained and the privacy of those tested is respected, that there is no coercion or manipulation, and that those tested are protected against stigmatization and discrimination.

4. An example from Iceland

Companies around the world that are involved in serious research in population genetics are dealing with the same or similar scientific and ethical issues. An example from Iceland would be the case of deCODE genetics. In

1996, Kári Stefánsson, an Icelandic born and trained medical doctor, having served for some years on the Neurology Faculty at the University of Chicago and Harvard University, founded deCODE genetics in order to pursue the genetic causes of human diseases. Though the company is incorporated in the State of Delaware, its corporate headquarters and major research facility is in Reykjavik, Iceland. There were several reasons for his choice of Iceland as a setting for this research: 1. Iceland has had a relatively homogenous population for most of the last 1000 years. It was very isolated until the middle of the 20th century, and also at the moment only 3% of the inhabitants are not citizens, and only 5% of the citizens are not native. 2. Nearly the entire genealogy of Icelanders is available based on historical records, back to the foundation of the nation in the 10th century. 3. In general, Icelanders are very educated and able to make informed decisions regarding participating in scientific work. 4. The country has – because of its socialistic governments in the past – a single-payer health care system with universal coverage. This makes discrimination based on genetics unlikely. Of course, Dr. Stefánsson's relationship with other Icelandic doctors and government officials was absolutely essential to the start up. Today, approximately 100,000 Icelanders have voluntarily participated in the research of deCODE genetics, providing blood samples for DNA and allowing the company to know and utilize their health information, usually restricted to one or a set of particular diseases. This unprecedented level of cooperation from over half of the adult population of Iceland is a testament to their confidence in the research, a confidence that is supported by the company's demonstrated commitment to publish the results of its investigations in scientific journals. The privacy of participants has also been secured by an ingenious encoding system that has been worked out between the company and the country's national ethics committee. DeCODE is a company first funded by a group of capital investors, but since 1998 publicly owned and traded on the Nasdaq stock exchange. Being publicly owned brings an obligation to report quarterly on its financial condition – this also increases public confidence. In addition to the capital raised when it initially went public, the company raises money for its research by applying for governmental grants and establishing contractual agreements with other pharmaceutical and biotechnology companies. Ultimately, deCODE hopes to be able to identify genetic mutations or polymorphisms that are associated with increased risk of disease. These variants can serve as the basis for genetic screening tests, and as the mechanisms of the disease are more fully understood, for the development of medicines for treatment. The sale of such products of research would provide the desired return on investment for the stockholders.

Among the diseases which are under investigation are traditional ones like non-insulin dependant diabetes mellitus, stroke, osteoarthritis, rheumatoid arthritis, prostate cancer, skin cancer, breast cancer, schizophrenia, bipolar disease, Parkinson's disease, Alzheimer's disease and hypertension. But the investigations also include such conditions as longevity, alcoholism and nicotine dependence. The company currently is involved in a clinical trial for a compound proposed to reduce the risk of myocardial infarction, and will begin clinical trials for medicaments to treat asthma and peripheral arterial occlusive disease later this year. There are two collaborations of note: one with Merck to study the underlying causes of obesity, and another with Hoffmann La Roche to develop diagnostic screening tests for certain diseases, including osteoporosis. Till now deCODE genetics, using genetic data, has identified 15 genes and drug targets in 12 common diseases. Gene regions have been identified in 16 other diseases and work is ongoing to identify those particular genes. DeCODE genetics is not involved in any stem cell research or human cloning experiments. It is also not currently aiming to develop any human gene therapies. The company has a commitment to science, and even ethical science, but not explicitly to a Christian ethic. No other genetics company to date has been as successful in its research. Perhaps this example of transparency in scientific reporting, transparency in financial reporting, protection of personal privacy, and positive interaction between the company and governmental and healthcare agencies is a model for genetic research in the current era.

5. Conclusions

There number of identified genetic variants associated with higher risks for disease is increasing rapidly. These variants are also getting easier and less expensive to screen – to the point that even screening entire populations for many diseases might become possible. This has the potential to produce enormous reductions in world-wide healthcare costs and great benefits to each individual's personal health. Thus, there should not be an *a priori* mistrust of such research and technologies. Several substantive obstacles, however, remain to be addressed. Much more work needs to be done, for example, to understand how each variant leads to the disease, and what treatments will be most appropriate for carriers of each variant. This will allow for a more rigorous assessment of the costs and benefits of a screening test. The population also needs to be educated in the use and limitations of genetic testing in general, and regarding particular screening they may be considering so that each person can make an informed decision. Regulations need to be enacted governing the production and sale of such tests, and establishing standards and safeguards against improper or unethical use of such screening and its results. This is especially important to prevent discrimination in the workplace or by health insurers. These scientific and legal issues are also clearly ethical issues. Each person needs to be treated with dignity. The motivations for the development of such tests needs to rest less

on financial rewards, or greed, and more on love and the desire for the betterment of the other. Here, the Church as "the Teacher of a way of life" of all children of God has her own responsibility and a good opportunity to inform and shape developing policies in this area of population genetic screening.

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11. In Utero Gene Therapy

Introduction:

Gene therapy is a relatively new therapeutic modality that has been developed over the last two decades, and is still under intense experimental investigation. Gene therapy can be defined as the process by which a normal functional copy of a gene is transferred into the appropriate cells of an individual with the intent to correct a disease caused by a defect within the individual's own copy of the gene in question.[1,2] Gene therapy promises to offer a precise means of permanently curing essentially any of the over 4000 diseases that are currently known to be caused by an error in only a single gene. These include but are certainly not limited to the hemophilias, lysosomal storage diseases like Gaucher's and Hurler's, hemoglobin disorders such as the thalassemias and sickle cell disease, diseases of immune function such as adenosine deaminase (ADA) deficiency, and cystic fibrosis. It is also anticipated that gene therapy will one day enable the treatment of a host of inherited or acquired disorders such as cancer, AIDS, and many others for which there is currently no cure. In contrast to existing therapeutic options such as protein replacement, which require lifelong therapy to prevent reemergence of disease symptoms, gene therapy promises to permanently cure disease by placing a healthy copy of the missing/genetically defective material in cells of the patient, which will ideally persist for a lifetime following a single treatment.

Since scientists and clinicians wish for a single treatment with gene therapy to provide a lifelong cure, much of the research on gene therapy has been focused on attempting to transfer the corrective genetic material into stem cells of the patients. Stem cells represent an ideal gene delivery "vehicle", since they possess the ability to self-renew, or divide to make two identical copies of themselves. This hallmark characteristic of the stem cell ensures that the stem cell pool within a person is not exhausted during their lifetime, and, from the standpoint of gene therapy, would guarantee that the patient would have a lifelong supply of genetically corrected cells. Another key aspect of stem cells that makes them ideally suited for gene therapy is their ability to differentiate to give rise to very large numbers of various different types of mature cells. If one thinks of the hematopoietic system, the vast potential of stem cells as a gene delivery vehicle becomes readily apparent. The turnover of cells in the hematopoietic system in a man weighing 70kg is close to one trillion cells per day.[3] This remarkable cell renewal process is supported by a small population of extremely rare cells normally found within the bone marrow of adults known as the hematopoietic stem cells, or HSC. These cells are capable of such extensive self-renewal that even small numbers of HSC can reconstitute the entire hematopoietic system of a patient after transplantation without exhaustion. It is this property of the stem cell which would enable a single successful gene therapy treatment to provide life-long correction of a genetic defect. Additionally, it is generally held that, in the steady state, only a few actively cycling HSC supply all of the hematopoietic cells at a given time. The ability to supply all of these cells reveals a second important characteristic of HSC, or stem ell in general; they are multipotential, i.e., capable of differentiating to produce all of the numerous types of mature blood cells in the circulation. These abilities to self-renew and to undergo multilineage differentiate combine to enable a single stem cell to produce hundreds of committed progenitor cells, which, in turn, give rise to thousands differentiated hematopoietic cells. Thus, even small numbers of genetically modified stem cells could exert a pronounced therapeutic effect in many genetic diseases.[4-6]

Limitations of Post-natal Gene Therapy

Unfortunately, at the present time, the successful application of gene therapy to the majority of candidate diseases has been hindered by several factors, many of which are related to the choice of HSC as target cells. The first of these is that HSC are normally in a quiescent state, which renders them resistant to genetic modification with the retrovirus-based vectors that are currently being used in many experimental and clinical gene therapy trials.[7] As a result of this, the levels of gene correction observed are very low. Another problem that has plagued post-natal gene therapy is the immune response to both the gene delivery vector and the protein that is produced. It is important to note that many patients suffer from the genetic diseases being targeted with gene therapy be-

cause they have never produced a single specific protein. As a result, their immune system has never "seen" this protein, and, following gene therapy, the cells of the immune system seek to eliminate any cells in the body that are expressing the very protein that could cure the patient of his/her disease. The low levels of gene delivery to stem cells and the immune response combine to yield very low levels of expression of the therapeutic protein, and even the small amounts that are produced are often only produced for a short time. Another major aspect of post-natal gene therapy that could limit its ability to provide a definitive cure is the fact that many of the diseases that could be treated with gene therapy exert a significant amount of irreversible damage to the patient prior to birth, during embryonic and fetal development. For example, irreversible neuronal damage is associated with inherited metabolic diseases such as Gaucher's, Lesch-Nyhan, and Tay Sachs. In these patients, post-natal gene therapy, while potentially capable of correcting the metabolic disorder, would be of only limited therapeutic benefit, since it could not reverse the damage which the gene defect had exerted during development. This is clearly in contrast to infants born with ADA deficiency or many other genetic disorders, who are essentially normal at birth, and could thus be cured by postnatal therapy. However, even in diseases which can be cured post-natally, scientific, psychological and financial benefits exist to argue for performing genetic correction in utero, since treating in utero would allow the birth of a normal healthy infant.

In Utero Gene Therapy

Several features of the developing fetus make it an ideal target for stem cell-directed gene therapy. During development, nearly all of the tissues of the fetus are undergoing tremendous expansion, and the stem cells within the various fetal tissues are included in this proliferative burst.[8,9] Thus, it is likely that fetal stem cells should be more amenable to retroviral-based gene transfer than their counterparts in an older patient. Another aspect of fetal development that makes early in gestation the ideal time for performing gene therapy is the tremendous expansion that occurs within the organ systems of the fetus during gestation. If even limited numbers of stem cells could

be corrected early in gestation, these cells should self-renew and differentiate to produce thousands of daughter stem cells and mature gene-corrected progeny, thus allowing even inefficient gene transfer into fetal stem cells to provide a substantial therapeutic benefit. A third key aspect of the early gestational fetus that bears mentioning is its immunological naïveté, which allows acceptance of cells and vector without the need for immunosuppression if transfer can be performed prior to thymic processing of mature lymphocytes. Furthermore, exposure to foreign antigens on cells/proteins during this period can often result in sustained immune tolerance, which can become permanent if the presence of the antigen is maintained.[10,11] The possible development of tolerance to the vector and gene product could theoretically permit postnatal treatment of the patient, if required, without the risk of immune rejection of the therapeutic cells and protein.

The Sheep Model

With the knowledge that performing gene therapy in utero would provide these advantages over existing post-natal approaches, we have spent the last 15 years exploring the possibility of performing in utero gene therapy using the fetal sheep as a model system. Sheep represent an ideal model for experimentally approaching the question of the feasibility of the in utero approach to hematopoietic cell gene therapy. In addition to its large size (which enables manipulation early in gestation), the sheep fetus shares many important physiological and developmental characteristics with the human fetus. For example, the pattern of fetal to adult hemoglobin switching, and the naturally occurring changes in the primary sites of hematopoiesis (from yolk sac to liver/spleen and bone marrow) are similar in both. In addition, the development of the sheep immune system has been investigated in detail, making the sheep an ideal model in which to study the immunological aspects of gene therapy.[12] Not surprisingly, the fetal sheep model has been used extensively in the study of mammalian fetal physiology, and results obtained with this model have been directly applicable to the understanding of fetal growth and development in other mammalian species including human.

The Cellular Approach

Our first attempt at in utero gene therapy in the sheep[13,14] utilized a stem cell transplantation-based method in which peripheral blood cells were collected from 110 day old fetal sheep (term: 150 days, exposed overnight to a retroviral vector containing the neomycin resistance (Neo®) gene, washed extensively, and then reinfused into the fetal sheep. Newborns were analyzed for the presence/expression of the vector sequences by both molecular and cell culture-based techniques. Over the 5-year course of these studies, the Neo® sequence was consistently detected in the marrow and blood of many of these animals, demonstrating that successful gene transfer into hematopoietic stem/progenitor cells with the ability to persist for

long periods in vivo had occurred.

These studies demonstrated that an in utero approach to gene therapy, at least in sheep, could result in the transfer and long-term expression of the vector-encoded genes with a higher efficiency than had been reported with other

large animal models. However, this technique possessed several potential shortcomings. The first of these was the amount of fetal manipulation that was required in order to obtain and re-infuse blood cells following in vitro gene modification. This manipulation led to three problems; a high degree of technical expertise was required to perform the procedure, the risk to the fetus was relatively high, and gene transfer could only be performed on older fetuses. This limits the usefulness of this technique to some degree, since by that point in development, an inborn error of metabolism would already have exerted much of its deleterious effects on a developing fetus.

The Direct Injection Approach

To overcome these shortcomings, we developed a new technique in which the gene transfer vector was injected directly into the peritoneal cavity of the developing sheep fetus. Our results thus far demonstrate that this approach is technically much simpler than the previous method, because it involves only a single injection into the peritoneum of the fetus, thus essentially eliminating any risk to the fetus. In addition, the injection can be given under ultrasound guidance, obviating the need for performing surgery on the mother to access the fetus, and greatly increasing the clinical applicability of the approach. In addition, it enabled us to perform the gene transfer at only 55 days, roughly half the fetal age of the cellular approach, improving the chances of achieving clinical benefit in diseases with early onset, and allowing induction of immune tolerance to the vector-encoded gene. Furthermore, placing the vector directly in the fetus should conceivably expose all of the various stem cells present within the fetus to the vector, rather than only those blood cells that could safely be removed, potentially increasing the levels of gene transfer to the desired target cells. Indeed, we have observed that the levels of gene transfer to the hematopoietic cells are several fold higher with this direct injection approach than with the prior cellular-based method, often achieving levels of 2-3% gene-marked cells in the circulation. Furthermore, by varying the age of the recipient at the time of gene transfer, we could markedly enhance the levels of hematopoietic cells that took up our gene therapy vector,[18] often obtaining transfer levels of 5-6% in the peripheral blood if gene transfer was performed at only 57 days of gestation (term: 150 days), a level that could exert a beneficial effect in at least some genetic diseases. Importantly, the fact that gene-marked cells have persisted in these sheep over the course of 5 years of study and that these marked cells engraft the hematopoietic system of secondary recipients upon re-transplantation provide evidence that this approach enabled us to successfully insert genes into the stem cells of the hematopoietic system, suggesting this method could provide lifelong genetic correction.

Not surprisingly, when we examined other tissues of the recipients we found that gene transfer was not limited to cells of the hematopoietic system, but had occurred in essentially all of the organs we examined, including numerous cell types within the liver and the lung.[15,16,19] While this finding raised the exciting possibility that this method could potentially be used to treat numerous genetic disorders that affect tissues other than the hematopoietic system, it also underscored the need to carefully examine the safety of this approach to gene therapy, since expression of the transferred genetic material in all tissues may not always be desirable, and, in some cases, could in fact be deleterious. Based on our observations in the hematopoietic system, we first examined whether the developmental stage of the recipient might impact upon which tissues were modified following in utero gene therapy. Our initial results revealed that the liver, like the hematopoietic system, is more amenable to gene transfer at earlier stages of fetal development, leading us to believe that perhaps gene transfer was always most efficient if performed earlier in gestation. However, when we examined the lungs of these same recipients, we discovered that this belief was unfounded. In the lungs we observed exactly the opposite of what we had seen in the hematopoietic system and the liver, namely, that the levels of gene-marked cells were much higher if the transfer was performed later in gestation, thus suggesting that each tissue likely possesses its own unique developmental stage during which gene transfer is optimal. These findings also indicated that perhaps the tissues to be modified could be chosen, to some degree, by the age at which the transfer was performed.[19]

While gene transfer to many of the fetal tissues might be desirable for correcting diseases that affect specific organ systems, our analyses also revealed that the fetal reproductive tissues often contained the gene therapy vector sequences, raising the troubling possibility that the developing germline might have been modified as a result of in utero gene therapy. We used three approaches to examine this important issue in detail:[20] 1) We performed immunohistochemical staining on tissue sections prepared from the

in utero treated animals; 2) We performed genetic analysis on the sperm cells from the treated males; and 3) We performed breeding experiments in a limited number of animals. These studies indicated that although the fetal ovaries appeared to be largely unaffected by in utero gene transfer, numerous cells within the developing fetal testes were in fact modified including interstitial cells, Sertoli cells, and small numbers of both immature germ cells within the forming sex cords and the resultant sperm cells. Importantly, however, gene-modified germ cells were only observed in 2 of the 6 animals examined, and, in these two animals, the incidence of germ cell modification was roughly 1 in 6250, a frequency that is well below the theoretical level of spontaneous mutation within the human genome.[21] This low frequency of modification coupled with observations that genetic alterations to the germ cells may produce deleterious effects,

placing them at a disadvantage during fertilization suggest that the likelihood that any genetic alterations present would be passed to subsequent offspring would be extremely unlikely. In agreement with this supposition, we did not observe transfer of the vector sequences in any of the 10 offspring we studied, even when both the parents had received gene transfer in utero. This is clearly an issue that will need to be addressed in greater detail, nevertheless, prior to moving in utero gene therapy into clinical trials.

Conclusions

In conclusion, we have provided evidence that in utero gene therapy possesses many advantages over postnatal gene therapy, both from a scientific standpoint and from a socioeconomic/psychological point of view, since it is one of the only therapies that could promise the birth of a normal healthy infant following prenatal diagnosis of disease. We have not observed any pathology as a result of this procedure, and the risk to the fetus appears to be minimal. We have demonstrated transfer and long-term (over 5 years) expression of the vector-encoded genes in many tissues of the recipient, suggesting that this approach could be useful in the treatment of numerous diseases affecting various organ systems. Nonetheless, as our studies thus far in the sheep model have highlighted, it is important to realize that in utero gene therapy is still in the experimental stages and many issues need to be clarified before a therapy of this type could ever be attempted in humans.

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12. International Bioethics and Human Genetics. The Activities of UNESCO

Due to globalisation, not only scientific and technological advances spread around the globe, but also bioethical issues. As the example of human cloning demonstrates, when a new technology has been developed in one country, it can be applied elsewhere, even if some countries want to ban its use. Medical research is increasingly multi-centre and international, with more and more research subjects recruited in developing countries. Also healthcare practices are global but guidelines and legal contexts differ and are sometimes absent. Rules for transplantation and procedures for organ donation, for example, vary among countries and these different approaches have led to abuses such as organ trafficking and the commercialisation of transplantation practices.

1. Standard setting in bioethics

Many countries, however, only have a limited infrastructure in bioethics, lacking expertise, educational programs, bioethics committees and legal frameworks. The global nature of science and technology implies the need for a global approach to bioethics. Member States have mandated UNESCO to set universal ethical benchmarks covering issues raised within the field of bioethics. They want to work together towards identifying basic principles and shared values regarding science, technology and health care. Standard-setting action in the field of bioethics has become a necessity that is felt throughout the world, often expressed by scientists and practitioners themselves, as well as by legislators, policy-makers and citizens.

It was in this context that in October 2003, based on preliminary feasibility studies, UNESCO was mandated by its Member States to draw up a declaration setting out fundamental principles in the field of bioethics. After two years of intense work, these same Member States adopted, unanimously and by acclamation on 19 October 2005, the *Universal Declaration on Bioethics and Human Rights*, thus solemnly affirming the commitment of the international community to respect a certain number of universal principles for humanity in the development and application of science and technology. With this new Declaration, UNESCO strives to respond in particular to the needs of developing countries, indigenous communities and vulnerable groups or persons, all of whom are the object of special mention throughout the text.

2. Standard setting and genetics

When UNESCO was considered by States to be the most appropriate forum for the elaboration of such a text, it was without doubt because the Organization has been able to confirm its standard-setting role in the field of bioethics. UNESCO, the only specialized instance within the United Nations system that combines education, culture, science and social sciences in its field of competence, has developed a bioethics programme over the past ten years that reflects the multidisciplinary and trans-cultural dimension of this debate. UNESCO is engaged in carrying out actions that involve all countries in this international discussion in order to bring out fundamental principles common to all, with respect for the cultural diversity of our societies. The success of the *Universal Declaration on the Human Genome and Human Rights* adopted in 1997 and the *International Declaration on Human Genetic Data* adopted in 2003 has reinforced UNESCO in its standard-setting action in the field of bioethics and has allowed States to place confidence in the Organization to finalize the Universal Declaration.

The *Universal Declaration on the Human Genome and Human Rights* formulates important principles to guide the development of genetic knowledge and the application of genetic technologies. A basic concept is that the human genome "underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity"; it therefore should be regarded, in a symbolic sense, as the "heritage of humanity" (Article 1). For this reason, the human genome in its natural state "shall not give rise to financial gains" (Article 4); it is also stated that benefits from advances in biology, genetics and medicine "shall be made available to all" (Article 12a).

The Declaration also emphasises the fundamental role of human dignity and human rights. This is a basic principle: "Everyone has a right to respect for their dignity, and for their rights regardless of their genetic characteristics" (Article 2a). This principle implies that genetic reductionism must be rejected; individuals cannot be reduced to their genetic characteristics. It furthermore implies non-discrimination; no one shall be subjected to discrimination based on such characteristics (Article 6). An important implication also is

that practices which are contrary to human dignity shall not be permitted; the text of this Article 11 explicitly refers to the reproductive cloning of human beings as an example of such infringement of human dignity.

3. The Universal Declaration on Bioethics and Human Rights

Under the aegis of respect for human dignity, human rights and fundamental freedoms, the *Universal Declaration on Bioethics and Human Rights* has a much wider scope than the previous Declarations that focused on genetics. It deals with ethical issues raised by medicine, life sciences and associated technologies as applied to human beings, taking into account their social, legal and environmental dimensions. The Universal Declaration aims to define universally acceptable norms, principles and procedures in the field of bioethics, in conformity with human rights as ensured by international law. It is thus conceived as a group of general provisions and principles that allow for a better evaluation of the implication of ethical issues at stake and to provide assistance in decision-making in this field. It does not seek to resolve all the bioethical issues presently raised and that evolve each day. Its aim is rather to constitute a basis for States wishing to endow themselves with legislation or policies in the field of bioethics. It also aims, as far as possible, to inscribe scientific decisions and practices within the framework and respect of a certain number of general principles common to all. And it aims to foster dialogue within societies on the implications of bioethics and the sharing of knowledge in the field of science and technology.

In order to achieve these goals, the Universal Declaration presents a vested right which is reflected in its title: it anchors the principles it endorses in the rules that govern respect for human dignity, human rights and fundamental freedoms. By drawing on the 1948 *Universal Declaration of Human Rights*, it clearly enshrines bioethics in international human rights law in order to apply human rights to the specific domain of bioethics.

Apart from the already well-established principles in the scientific community such as informed consent, the principle of autonomy and individual responsibility, respect for privacy and confidentiality (also articulated in the two previous Declarations adopted by UNESCO), the *Universal Declaration on Bioethics and Human Rights* raises the issues of access to quality health care and essential medicines, nutrition and provision of clean water, to the improvement of living conditions and the environment and the reduction of poverty. The Universal Declaration thus opens perspectives for action that reach further than just medical ethics and reiterates the need to place bioethics within the context of reflection open to the political and social world. Today, bioethics goes far beyond the code of ethics of the various professional practices concerned. It implies reflection on the evolution of society, indeed world stability, induced by scientific and technological developments. The Universal Declaration paves the way for a new agenda of bioethics at the international level.

4. Towards international bioethics

Although the Universal Declaration constitutes a non-binding instrument in the eyes of international law, its value and its strength are in no way diminished. For the first time in the history of bioethics, all States of the international community are solemnly committed to respect and implement the basic principles of bioethics, set forth within a single text. Also through the Universal Declaration, bioethics finds its place on the agenda of States. Furthermore, characterized by the transparency and active participation of all the actors concerned, the elaboration process of the Universal Declaration, involving extensive consultations, has already largely contributed to the renown of the text and its general acceptance. The innovative dimension of the Declaration is that it constitutes for the first time a commitment of governments to a set of bioethical principles. Previous international declarations, although sometimes very influential, such as the *Declaration of Helsinki*, have been adopted by professional organisation (such as the World Medical Association).

The timetable set out for the elaboration of the Declaration planned a first year devoted to the drafting work of the International Bioethics Committee of UNESCO (IBC) – a UNESCO advisory committee composed of independent experts – and a second year devoted to intergovernmental negotiations on the basis of the text drawn up by IBC. Nevertheless, broad consultations, hearings and conferences were carried out worldwide throughout the process of elaboration in order to associate

States, other specialized agencies of the United Nations system and other intergovernmental organizations, non-governmental organizations voicing in particular vulnerable persons and groups, relevant national bodies and specialists. By means of the Internet site that permitted the results of each meeting or consultation held to be made public and regularly posted online, all were free to present their views, remarks and comments to IBC on the different versions of the text. Thus, from the very beginning of the elaboration process, the Universal Declaration has promoted general recognition of bioethical concerns and has stimulated the bioethics debate in the four corners of the world, involving and nourishing intercultural dialogue on these issues.

5. Conclusion

The Universal Declaration on Bioethics and Human Rights should be seen therefore not as the fruit of the reflection of just a few but as the result of a long and sustained common effort in which all relevant actors have been involved. It is also the first normative instrument that has been adopted by Member States and therefore expresses a commitment of governments in the area of international bioethics. The principles articulated in the Universal Declaration are in some cases already expressed in previous Declarations adopted by UNESCO but the scope of these principles have now been widened in order to cover medicine and life sciences as a whole. Other principles articulated in the Universal Declaration are relatively new. They cover a broader area of interest, not only of more developed countries but also particularly of less developed countries, taken into account diverse cultures, religions and schools of thought.

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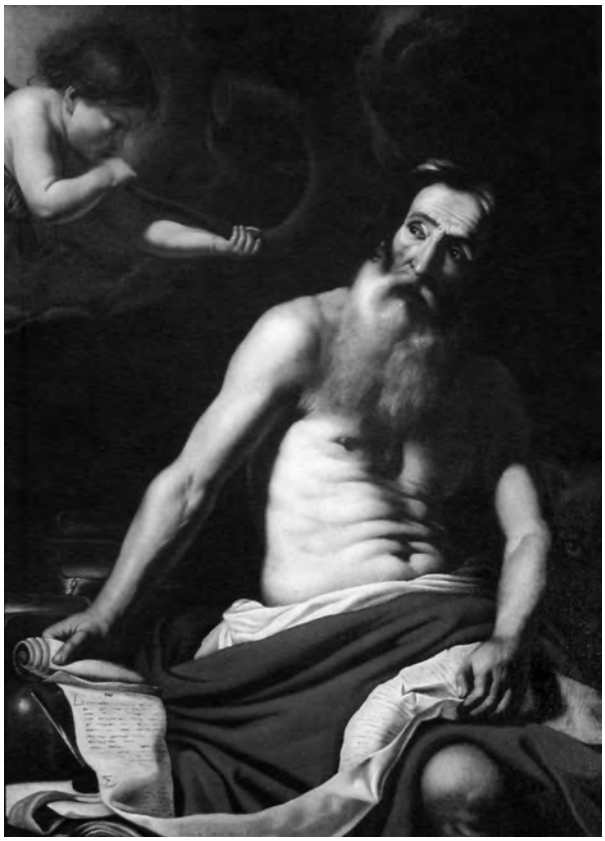
Notes

Further information on the Universal Declaration and the process of its elaboration, can be found on Internet at the following address: *www.unesco.org/bioethics*



CELESTINO MIGLIORE

13. Genetic Research and International Co-operation

At the same time as joining the chorus of congratulations expressed to the untiring organisers of this important conference, I would like to thank Cardinal Javier Lozano Barragán for inviting me to give a paper. This is an invitation that honours me and takes me back to some of the most intense professional moments of my service to the Holy See: the debate on, and the adoption of, the Convention on Biomedicine and Human Rights of the Council of Europe, which I followed personally between 1992 and 1995 at Strasbourg, and the resolution of the General Assembly of the United Nations on human cloning which was adopted last March. From the early days of my mission to the United Nations I have been a direct participant in this debate, which, indeed, we have pursued with tenacity and passion. In three years of activity at the United Nations I have never seen a meeting hall so full, in terms of the number, and high level, of the delegations, and I would also say one so suffered. One really had the impression, and also the satisfaction, that one was witnessing one of the debates of the century.

1. The Recognition of the Regulating Process of International Co-operation in Genetic Research

In order to outline a general framework of the principles and provisions that make up and regulate international co-operation in genetic research one needs to present a survey, albeit necessarily of a summarising character, of the regulating processes in this field.

Given that the subject of my paper is 'genetic research and international co-operation', I would like first of all to outline the subject under examination. The topic of genetic research covers two different fields – vegetal and animal genetics, on the one hand, and human genetics, on the other. These are two separate fields and in relation to them both international law follows a bifurcation as well. Vegetal and animal genetic research is governed by the Convention on Biodiversity which does not apply to human genes but to vegetal and animal genes alone. Human genetics and the questions and problems

connected with the defence of human rights are instead dealt with in the Universal Declaration on the Human Genome and Human Rights and the Universal Declaration on Bioethics and Human Rights of UNESCO, in addition to the Convention on Biomedicine and Human Rights of the Council of Europe and the recent Protocol on Biomedical Research which forms an appendix to this Convention. The context of my paper – that is to say this international conference on the human genome – leaves no doubts as to what is to be addressed. I will thus devote myself solely to international co-operation in relation to human genetic research.

In the international context, beginning with the Code of Nuremberg of 1947 until the International Ethical Directives for Biomedical Research Carried out on Human Beings which was drawn up in 1993 by the Council for International Organisations of Medical Sciences (CIOMS) in conjunction with the World Health organisation (WHO), various recommendations, laws and reports followed one another. However, the leading role in this area is UNESCO with its Universal Declaration on Human Genome and Human Rights, which was adopted in 1997.[1]

2. Principles and Provisions

a. The International Context: UNESCO

In fundamental terms, the Declaration of UNESCO presents a framework of principles designed to achieve a balance between assuring respect for fundamental rights, on the one hand, and the need to assure freedom of research, on the other. As regards the subject of this paper, we encounter, however, a very important statement which after a certain fashion underlies, motivates and encourages international co-operation in the field of genetic research. Article 1 states that 'the human genome underlies the fundamental unity of all the members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense it is the heritage of humanity.' There are three statements here that warrant examination. First of all, the scientific, cultural and juridical co-operation involved has its foundation in the unity of all the members of the human family

which is indicated by the genome itself. To assert that this also underlies a recognition of the dignity and diversity of human beings seems to mean that a person finds his or her foundation in the specific dignity of the genome. 'In reality' as one can read in the Note of the Secretary of State of the Holy See of 24 May 1998, 'it is the dignity of man and the unity of the human family that bestow upon the human genome its value and require that it is protected in a special way'.[2] In this sense, international co-operation is also invested with this special value, task and service. The foundation of international co-operation is then reinforced with the statement that the human genome is a heritage of humanity. The Note Explaining the Declaration makes clear that this formulation intends to mean the responsibility of the whole of humanity, with the exclusion of any collective appropriation of it (n. 20). Here also I think that it is useful to cite the pertinent observation to be encountered in the above-cited Note of the Secretariat of State: 'However the sentence remains vague and not very clear. It would be better, avoiding notions such as 'heritage of humanity', to state that 'the whole of humanity has a special responsibility to protect the human genome'. In addition, the genome has two dimensions: a general one, in that it is a characteristic of all those who belong to the human species, and another individual one, in that it is different for each human being, who receives it from his parents at the moment of conception – it is in this last sense that one commonly refers to a 'genetic heritage' of the human being. It appears clear that it is to this 'heritage' that one must apply a fundamental juridical protection because this 'inheritance' applies concretely and individually to each human being'.

At a more specific level, the Declaration on the Human Genome dedicates three articles (nn., 17, 18, 19) to solidarity and international co-operation as regards genetic research. Solidarity should be practiced at two levels: at a personal level, that is to say by allowing individuals, families and groups that are especially vulnerable to, or affected by, diseases of a genetic nature to take advantage of their rights in full freedom and dignity; and at a public level, which imposes on states the duty to foster the diagnosis, prevention and treatment of genetic diseases, and in particular rare and endemic genetic diseases which afflict broad sectors of the world's population. The text then emphasises scientific and cultural co-operation in the fields of the human genome, human diversity and genetic research, making clear that the goal is to assess the risks and benefits of genetic research and to prevent possible examples of abuse. It is also said that the benefits of research, developed above all in developed countries, must serve to promote economic and social progress for everyone. The subsequent Directives on the Implementation of the Declaration encourage co-operation between the North and the South of the world and envisage that the International Bioethics Committee will periodically assess and remove any possible obstacles to this.

Of especial importance are the reports of the International Bioethics Committee, once again produced by UNESCO. I will only refer to those that are most relevant to the subject of this paper.[3] The Report on Bioethics and Human Population Genetics Research, which was drawn up in 1995, although its offers principles and orientations for gene therapy with a specific aim, also makes warnings and calls for juridical measures in order to avoid an improper and unacceptable use of genetic research for discriminatory, commercial or deterministic purposes.

The Report on Solidarity and International Co-operation between Developed and Developing Countries Concerning the Human Genome is probably the most extensive and complete text on the subject of this paper. It devotes an entire section to solidarity and international co-operation in matters connected with the human genome. With respect to genetic research, it recognises that this assumes the existence of investments, technology and highly specialised personnel and encourages international organisations, the World Bank and regional banks, as well as developed countries, to create international mechanisms and funds by which to support research in countries which would not otherwise be able to afford it. The list of systems for bilateral, multilateral and regional co-operation already existent in this sector is very illustrative, even though the conclusion has a bitter taste: 'States rapidly recognised the implications of the new scientific advances, but they have not always been so prompt in undertaking projects of solidarity and international co-operation as set out in the Universal Declaration on the Human Genome and Human Rights.'

The Report on Human Genetic Data: Preliminary Study by the IBC on its Collection, Storage and Use, which was published in 2002, emphasised that the new conditions in which genetic research was being carried out, and in particular the growing involvement of the private sector, the increase in basic human genetic data, the at times controversial nature of their use, the variety of the parameters adopted by international research, and the urgent need to protect vulnerable populations in the collection of genetic data, all required a new and adequate international instrument in this field. The same observation and recommendation is to be found in the explanatory Report on the Possibility of Elaborating Universal Instrument on Bioethics of 2003.

As a result, an Intergovernmental Meeting of Experts for the Revision of the Text of the Universal Declaration on Bioethics and Human Rights was created which last June, in Paris, held its second session of deliberations with the aim

of completing the text and subjecting it to the approval of the thirty-third General Conference of UNESCO.

As regards the subject of this paper, it is interesting to begin with the debate on the title of the new instrument. The proposal that was developed with the ICB was to entitle that instrument 'Declaration on Universal Bioethical Rules'. Hesitation about establishing rules in such a delicate and controversial field led to the adoption of a less demanding title and one anchored in human rights – The Universal Declaration on Bioethics and Human Rights.

In this text, which was adopted with acclamation last October,[4] notable emphasis is given to international co-operation, a subject addressed in at least three chapters. Where reference is made to the sharing of benefits (art. 15), it is declared that the benefits derived from scientific research and its application 'should' be generally shared within society and the international community, and in particular with developing countries. This is a holistic statement but one in a flat key. The verb 'should' is used and not the simple future tense 'shall', which, in juridical language as well, has an imperative meaning. On this point, if one compares the Declaration on the Human Genome and the project of the Universal Declaration on Bioethics and Human Rights, it becomes immediately evident that whereas the first makes an almost regular use of the word 'shall', the second very much employs 'should'.

In addressing practices at a transnational level, article 21, once again employing the word 'should', declares that transnational research in this field should take into account the needs of the country where it is carried out and recognise the importance of contributing to dealing with urgent questions connected with health and of a global character. In addition, it suggests fair participation in the profits from research for all the parties that sign a contract or agreement. Article 24 is entirely devoted to international co-operation but again the word 'should' is employed.

a. States should foster the international dissemination of scientific information and encourage the free flow and the sharing of scientific and technological knowledge.

b. Within the framework of international co-operation, States should promote cultural ad scientific co-operation and enter into bilateral and multilateral agreements enabling developing countries to build up their capacity to participate in generating and sharing of scientific knowledge, the related know-how and the benefits thereof.

c. States should respect and promote solidarity between and among States, as well as individuals, families groups and communities, with special regards for those rendered vulnerable by disease or disability or other personal, societal or environmental conditions and those with the most limited resources.

It is clear that this Declaration reflects the recommendations of the International Bioethics Committee and constitutes a step forward in the codification of rules concerning co-operation in genetic research.

b. The International Context: the General Assembly of the United Nations

In the international field, the initiative continues to be held in large measure with UNESCO. It should, however, be pointed out that the United Nations adopted the Universal Declaration on the Human Genome by a resolution of the General Assembly of 1998.[5] References to international co-operation in broader fields which include genetic research can be found in the Resolution on Human Cloning which was adopted last March[VI] where members States are invited to include the global questions of AIDS, tuberculosis and malaria, which in particular affect developing countries, in programmes that fund medical research and the life sciences.

c. *The Regional Context: the Council of Europe*

At a regional level, the cornerstone continues to be for the time being the Convention on Biomedicine and Human Rights of the Council of Europe which was adopted on 19 November 1996[7], with the Protocol on Biomedical Research that was appended to this Convention and opened to being signed on 25 January last.[8] This Convention outlines a broad series of fundamental principles and rules that constitute the basis of shared European law on medical bioethics, the defence of human rights and the medical sciences. International co-operation is mentioned in the preamble as a need directed towards ensuring that the whole of humanity draws advantage from the benefits of biology and medicine. In the articles a special section is devoted to the public debate on questions of biomedicine and its applications which, although located within the States signing the Convention, constitutes an important elements as regards international co-operation as well.

Of notable importance are the solutions adopted by the Protocol which devotes an entire section to research carried out in States that do not adhere to this juridical instrument. In the explanatory Protocol[9] one reads: 'At the present time a large number of research projects are carried out on a multinational basis. Individual projects can be followed by groups of researchers of different States. In addition, organisations with an international status can choose in which State to carry out a project began and financed by them. This raises certain worries given the possibility that the rules for protection applied to participants vary substantially from one country to another. The possibility that research that is considered decisively unacceptable for one State is carried out in another State that adopts rather fluid criteria provokes especial concern'.

Article 29 thus lays down the conditions to be followed by the sponsors and researchers of an adhering State that want to carry out or finance research in a State that does not adhere to the Protocol. In substantial terms, they must respect the conditions dictated by the host country but they must also respect also the principles on which

the provisions of this Protocol are based. Reference is made to underlying principles and not to concrete provisions because it is often the case that these latter, because of the diversity of situations, are not actually feasible. The explanatory report gives the example of independent requests for the scientific and ethical assessment of a specific programme. Even though these may not exist in the host country, obedience to the principles laid down in the Protocol requires that such a scientific and ethical assessment is carried out by a qualified and independent body. This also applies to the principles of informed consent, the protection of the incapable, confidentiality, and the risk-benefit ratio.

The same protocol also establishes another provision that is relevant to co-operation in general and international co-operation in particular. Article 28 enjoins researchers to submit a report or a summary of their research to their respective ethical committees or relevant body and to publicise the results of their research even when this has negative results. The publication of these results is to be considered done when it is accessible to other researchers. Indeed, the aim of this article is to avoid the useless repetition of research on people and the suppression of its results, whether they are positive or negative, for commercial or anyway non-scientific ends.

H.E. Msgr. CELESTINO MIGLIORE
Apostolic Nunzio
Permanent Observer of the Holy See
at the United Nations.

Note

[1] This document can be found at *http://portal.unesco.org/shs/en/ev.php-URL_ID=1881&URL_DO=DO_TOPIC&URL_SECTION=201.html.*

[2] Cf. *http://www.paginecattoliche.it/modules.php?name=News&file=article&sid=694*

[3] Reference is made here to the reports published on the Internet site of UNESCO *http://portal.unesco.org/shs/en/ev.php-RL_ID=2038&URL_DO=DO_TOPIC&URL_SECTION=201.html: Report of the IBC on the Possibility of Elaborating a Universal Instrument on Bioethics (2003)*, rapporteurs: Giovanni Berlinguer and Leonardo De Castro; *Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention (2003)*, rapporteur: Hans Galjaard; *Human Genetic Data: Preliminary Study by the IBC on its Collection, Processing, Storage and Use (2002)*, rapporteurs: Sylvia Rumball and Alexander McCall Smith; *Report of the IBC on Ethics, Intellectual Property and Genomics (2002)*, rapporteur: Judge Michael Kirby; *Report of the IBC on Solidarity and International Cooperation between Developed and Developing Countries concerning the Human Genome (2001)*, rapporteur: Mehmet Öztürk; *The Use of Embryonic Stem Cells in Therapeutic Research (2001)*, rapporteurs: Alexander McCall Smith and Michel Revel; *Report on Confidentiality and Genetic Data (2000); Report of the Working Group of the IBC: Ethical Considerations Regarding Access to Experimental Treatment and Experimentation on Human Subjects (1996)*, rapporteurs: Harold Edgar and Ricardo Cruz-Coke; *Food, Plant Biotechnology and Ethics (1995)*, rapporteur: Darryl Macer; *Bioethics and Human Population Genetics Research (1995)*, by Chee Heng Leng, Laila El-Hamamsy, John Fleming, Norio Fujiki, Genoveva Keyeux, Bartha Maria Knoppers and Darryl Macer; *Genetic Counselling (1995)*, rapporteur: Michel Revel; *Ethics and Neurosciences (1995),* rapporteur: Mr Jean-Didier Vincent*; Report on Human Gene Therapy (1994)*, rapporteurs: Mr Harold Edgar and Mr Thomas Tursz; *Report on Genetic Screening and Testing (1994)*, rapporteur: Mr David Shapiro .

[4] Cf. *http://portal.unesco.org/shs/en/file_download.php/b0f1e8f1dc4a4e8990faff370608cac2declaration.pdf*

[5] A/RES/53/152, 9 December 1998.

[6] A/RES/59/280, 23 March 2005.

[7] Cf. *http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm*

[8] Cf. *http://conventions.coe.int/Treaty/EN/Treaties/Html/195.htm*

Second Session

Illumination

Friday
18
November

VINCENZO CAPPELLETTI

1. The Historical Journey of Human Genetics

'The new developments that take place every so often in science generally have their origins in the invention of a new method, in the discovery of a new fact from which relevant consequences flow, or in the drawing up of a new theoretical principle which suggests new lines of research… The case of genetics does not correspond to any of these three alternative possibilities, given that genetics began with the discovery of a discovery that had taken place thirty years previously. We may, in fact, date the birth of genetics to the rediscovery in 1900 of Mendel's article'. Thus wrote Thomas Hunt Morgan, director of the research group on the *Drosophila* (the fruit fly), who was at Columbia University of New York before moving to the California Institute of Technology, as well as the promoter of the connection between cytology and Mendelism, in the periodical *Science* in the year 1932.[1] The judgement that has just been quoted possesses the defect of excessive simplification. Why, we may ask, did the rediscovery of Mendel not meet with the same fate as the discovery made by Mendel? It is true that the personalities involved were famous: the German Carl Correns (1864-1933), the Austrian Erich Tschermack (1871-1962) – both botanists – and the Dutchman Hugo de Vries (1848-1935), a plant physiologist and in later years the author of an extensive work on 'mutation'.[2] But the authors just cited, in rediscovering Mendel, gave to his observations the broad context that had not existed thirty years previously and placed them within 'biology' – the theory of life in general and of man in particular, according to the incisive definition of a term that had entered use at the beginning of the century as a result of the work of the physiopathologist Rudolf Virchow.[3]

The answer to the question that has just been posed is thus to be found in the relationship between the conceptual-topical history and the observational-experimental history of scientific research. When the two essays of Gregor Mendel (1822-1884) were published in the *Verhandlungen* of the Moravian Union of the Naturalists of Brünn (the first and most well known was on *Pisum sativum* (1866), the second, published in 1869, was on *Hieracium*), with their description of the dominance, the independence and the segregation of characteristics, the life sciences were experiencing an intense season of new ideas that centred round the 'theory of descendance', 'the theory of cells' and the notion of 'physiopathology' as a synthesis of normality and illness – a broad arch of subject matter that went from traditional natural history to the emerging reality of biomedicine. In 1859 Charles Darwin's *On the Origin of Species* sold out immediately after publication in the space of a day, and when Darwin was still alive his work went into six editions.[4] The last edition was published in 1872 with very significant changes and additions. Darwin observed in the final chapter that embryology would reveal the partly obscured structure of the prototypes of each great class. And he concluded by referring to the grandiose aspect of a conception of life, with its various forces, at the outset breathed by the Creator into a few forms. But the work of Darwin which may be considered the most important as regards the advance of the general theory of living things was that published in 1868, namely *The Variation of Animals and Plants under Domestication*.[5] In the view of this scientist, the features and structures of organisms changed because of an intrinsic property or force or according to specific laws when the variation involved more than one organ or functions, when it is, that is to say, it was 'correlated'. Jean Baptiste Lamarck in his *Zoological Philosophy* of 1806 had argued that that environment provoked modifications in organisms which could be transmitted to their descendants by acting on 'interior feeling', where a 'feeling organ' existed, or simply through an intensification of their use. The extension of the neck in giraffes, which are forced to browse on the leaves of trees in environments without grass, was the case that Lamarck, an acute naturalist and a high-level malacologist, had cited to support his theses regarding such transformation. For this scientist, in the individual that was transformed there was the species and in the species there was nature, from which all bodies organised 'with the help of sufficient time' drew their origins. A dual series of transformations, therefore: natural transformations of a creative kind and adaptive transformations of an individual and specific kind.

A new perspective was opened up for the life sciences with Lamarck around the question of 'transformation', 'descendance' and 'evolution' characterised by the proposal to

leave Linneo behind and to replace his classification of animals and plants with a history of nature that was really such and upon births, deaths and life-spans, on increases in terms of substance and increases in terms of structures. The uniformistic geology of Charles Lyell (1797-1875), with the eleven editions of his *Principles* between 1830 and 1875,[6] had supplied the paradigm based on transformations with an ingredient that was neither unique nor even sufficient but which that was without doubt indispensable – time. Thousands of years had become millions. Despite vigorous and rigorous opposition, in the name above all else of original structural diversities to be found in both the animal kingdom and the vegetable kingdom of living nature; after *On the Origin of Species* of Darwin had replaced the *Zoological Philosophy* of Lamarck; and after acquiring new prestige in Ernst H. Haeckel (1834-1919), the 'prophet of Jena', transformism was able to celebrate in the 1860s, the decade of the essays of Mendel, its own high noon and to experience a triumph that was held to be irreversible. In 1868 Haeckel published his *History of Natural Creation*, which was translated into eleven languages and it is to Haeckel that we must attribute the merit of having openly declared the ultimate implication of transformism – the ability to obtain being from non-being, the ability to create, removing it from the God of Linneus, as indeed Haeckel explicitly declared, and attributing that ability to the reality of space and time, and thus to the world. Darwin did not follow him along this path (indeed, to be precise, he had not preceded him along this path): very many aspects and moments of nature did not seem to him to be traceable to a transcendent design but he held that it was difficult to see 'this wonderful universe and in particular the nature of man' as the result of brute force, as he wrote on 22 May 1860 to the American botanist Asa Gray. Although Herbert Spencer (1820-1903) gave to the term 'evolution' a meaning that was opposed to its original pre-formistic meaning, involving the move from the non-developed to the developed, and thus from the small to the large, in his *Principles of Biology* of 1864,[7] Spencer was cautious enough to refer to a hidden Unknowable cause behind reality.

The years when Gregor Mendel (1822-1884), an Augustinian monk who was by now in his forties after studying the natural sciences at Vienna without obtaining a degree and who had a very strong interest in physics and logical formalism as well as hours of free time each day to dedicate to the monastery garden, published the above mentioned essays, were years of giants. The results of Mendel's work were relevant and to such an extent as to define heredity as a discontinuous process in opposition to what Darwin and the biometrician Francis Galton (1822-1911), the highest authority of the time on the quantitative-statistical aspects of biology, thought. Mendel affirmed that hybrids were bearers of dual hereditary determinants for a specific character which became segregated in the second generation

and could recombine according to various possibilities. For this scientist, pairs of distinct characteristics behaved in an autonomous way in hybridisation. Mendel's protocols were important and were presented with exemplary clarity but without a context, something that was all the more necessary at a time when science was encountering a series of major problems. There is a reference to Darwin in the text of the first essay by Mendel but this is no more than a reference. Mendel was in contact with the distinguished botanist Carl Wilhelm Nägeli (1817-1891) who was interested in the distinction between the different parts and functions of cell plasma, beginning with a mechanical approach, indeed an mechanistic approach, an approach which entered an irreversible crisis just as he published in 1884 his *Physiological-Mechanical Theory of Filiation*.[8] The term that the author uses is no longer 'descendance' but '*Abstammung*', which would appear to indicate the creation of a paradigm that was distinct from the theory of evolution. *In nuce* it was the theory of heredity which at the end of the century would be able to rediscover the discovery made by Mendel. In the meantime, attention continued to be directed towards the creation of a conceptual context, and this was helped by a revival of the dialectical dialogue between the great perspectives on the 'world of life', to employ the enlightening phrase coined by the phenomenologist Edmond Husserl in his *Crisis of the European sciences.*[9]

In the foreground we encounter the 'theory of cells', a theory linked to the name of Rudolf Virchow (1821-1902), and to the prestige obtained by this scientist through his synthesis of physiology and pathology in biology understood as the 'doctrine of life in general and man in particular'. Virchow's *Cellular Pathology* had been published in 1859,[10] but in the 1870s it was proposed again as a programme of research in order to cover the difficult territory of neoplasias. If all life was cellular, then *Deszendenz* and *Abstammung*, evolution and filiation, could not but introduce the cell into the process of ontogenetic and philogenetic construction as a foundation and a reference. Reference has already been made to Nägeli as an interlocutor of Mendel: his was the distinction between nutritive 'trophoplasm' and the 'idioplasm' as the carrier of specific characteristics. But the already cited *Theory of Filiation* was published in 1884, a year after the essay of August Weismann (1834-1914) entitled *On Heredity*.[11] This publication not only marked the birth of the scientific paradigm that would later be called genetics but was also a rational turning point for the whole of biology, including the theory of cells. A medical doctor at the outset but from 1867 onwards professor of zoology at Friburg, and a fervent Darwinian, Weismann acutely felt the antithesis between Darwin's approach and that of Lamarck, and he overcome this antithesis by approaching the problem in terms of cells. A cell, declared Weismann in a decisive way, did not contain any structure that demonstrated that it was made to incorporate acquired characteristics and to transmit them to descendants. In this way, a simplified reading of life and living things was superseded, a con-

cession to the common sense that had seduced the majority of naturalists, including the author of *On the Origin of Species,* and to which Weismann had been inclined before the essay that has just been cited was published. Employing 'variation' understood in the sense employed by Darwin, Weismann came, instead, to infer the autonomy and the continuity of the germinal plasma during the course of successive generations. In this way was born one of the broadest, most rigorous and most counter-intuitive – to use a term of contemporary logic – perspectives in the history of science. And a subsequent essay of 1892, entitled *On Germinative Plasma: a Theory of Heredity*,[12] marked the birth of a cognitive paradigm which in 1906, in response to a proposal made by the zoologist William Bateson (1861-1929), a professor at the University of Cambridge, would come to be called 'genetics'.

In the meantime Mendel had been rediscovered in 1900 by the three botanists to whom reference has already been made: Bateson working on chickens and Lucien Cuénot (1856-1951), of the University of Nancy, working on mice, extended the Mendelian approach to the animal kingdom. Botany came back into the picture with the classically rigorous research of the plant physiologist of Copenhagen, Wilhelm Ludvig Johannsen (1857-1927), on the variability of beans: the differences in size and weight, he affirmed, derived from environmental causes and were not inherited. This amounted to an experimental confutation of the theories of Lamarck that was consistent with the approach of Weismann and the context of the experiments carried out by Mendel. Mendel's protocols had come to form a part of a complex and compact theoretical construction which had made them significant and also facilitated their rediscovery. The convergence of the theory of evolution and the theory of cells had been the starting point for this, and at the level of the fecundity of knowledge of both these phenomena this convergence had not been exhausted. At the turn of the century the botanist Edouard Strasburger (1844-1912) of Bonn, and the anatomist Walter Flemming (1843-1905) of Prague and Kiel, returned to the question of the reproduction of cells which had already been studied and described by Virchow – the fundamental cytogenetic principle *Omnis cellula e cellula* had been formulated by this scientist – with his account of the division of the nucleus or 'karyocinesis', the presence of 'chromosomes' in the nuclear substance, and their fission and migration into the newly formed cells. Edouard van Beneden (1846-1910), a professor at Leida and at Lieges, observed and described 'meiosis' in the germinal cells, a process where the number of chromosomes is reduced by a half in order to come together again with the appearance of homologous chromosomes at fertilisation. In fertilisation, as was discovered in 1875 by Oskar Hertwig (1849-1922) of the University of Berlin when studying see urchin eggs, the male and female gametes fuse into a single nucleus.

In this field knowledge through observation and its theoretical elaboration followed on their course well beyond the axiom of Virchow cited above: within cytology 'karyology' was formed, a specific paradigm of knowledge as regards the cellular nucleus, its functions and its behaviour. At this point not only was it possible to rediscover Mendel but it was also possible to locate and give a structure to the 'hybridisation' that he had analysed and formalised with such admirable clarity. Of German origins and development until the turn of the century, with an unexpected deviation cytology crossed the Atlantic and brought with it not only the most recent results at the level of observation regarding the division of cells, the nucleus, and chromosomes, but also the problematic nexus with embryology. This was because of contrasting positions in relation to the development of a fertilised frog egg: the 'mosaic' pre-formation of Wilhelm Roux (1850-1924) and the regulation inherent in an 'equipotential harmonious system' of Oskar Hertwig (1849-1922) and Hans Driesch (1867-1941). Another rich source of developments at the level of concepts, received in various ways in America, was to be found in the theoretical formulations of Morgan who had fallen back into a condition of disturbance of his eyesight which prevented him from employing the microscope. For this scientist, the chromosomes of the gametes had to undergo a 'reductive division' in order to conserve the specific number of the species after being recombined in fertilisation. This brilliant hypothesis, which had already been confirmed by the above mentioned discovery of meiosis, was accompanied by another, by Weismann once again, about the 'determinants' located in the chromosome plasma which acted upon the morphofunctional characteristics of the organism. This was a step towards the search for, and recognition of, 'genes' – the term would be proposed by Johannsen in his *Elements of an Exact Doctrine of Heredity*, which was published in 1909 and republished again on a number of occasions.[13] The interaction between cells and heredity was advanced in such terms once again at the Columbia University of New York after the above mentioned migration, although perhaps it would be more accurate to say propagation, of research at the level of cytology. The cytologist of this American university was Edmund B. Wilson (1856-1939). After a composition which took a long time, his volume *The Cell in Development and Heredity* was published in 1896. It would be republished again in 1900 and 1925 and would come to be a new reference book in Europe as well.[14] The chromatynic mass with its unknown meaning, which had been identified by previous scholars and thus given the letter 'X', was identified by Wilson with the sexual chromosomes or 'heterochromosomes', which were different in males and females. The next step could only be the location of the genes in the chromosomes, or at least an attempt in that direction. Basing himself on the demonstrated relationship between chromosomes and sexuality, Wilson encouraged the research of the zoologist Thomas H. Morgan (1866-1946), who was initially opposed to the approach of Mendel and the theory of chromosomes, approaches suspected of preformism by a researcher who looked with favour on the epigenistic positions of the embryologist Driesch. As subjects for experiments, rats and pigeons were replaced by the fruit fly, *Drosophila melanogaster*, which has a brief lifecycle and a minimal culture space. From this new subject matter for experiments there arose an established link between specific characteristics and sexual chromosomes – in the variant male *Drosophila* with blue rather than red eyes a linkage was demonstrated between the determinant of sex and the determinant of eye colour. The emer-

gence of other similar variants was matched by an intensification of the research planned and carried out by Morgan with his pupils Alfred H. Sturtevant (1891-1970), Calvin B. Bridges (1889-1938), and Hermann Joseph Muller (1890-1967) – the so-called *Drosophila* group. Mendel's theory of chromosomes triumphed over the alternative approaches proposed by Bateson, who was nonetheless a convinced follower of Mendel but with relevant adaptations at the level of partial, polygene and quantitative heredity. With what were called genes there arose the central problem of a paradigm which by now had a name and a broad experimental and theoretical autonomy. In 1915 a large volume by Morgan together his above-listed collaborators was published: *The Mechanism of Mendelian Heredity*[15], which was followed in 1926 by *The Theory of the Gene*[16] and in 1933 by the award of the Noble Prize. These were events that crowned, beyond personal success, a long trajectory from which was born a project of knowledge in natural science.

With the localisation of the genes in the chromosomes the Morgan group of Columbia University had obtained the connection between the theory of hereditary processes and the cellular paradigm. But another necessary correlation had to be looked for - with the evolutionary paradigm. In 1890 Morgan had visited the zoo of Naples where he had met Driesch and established a programme of research on the embryology of ctenophores and other groups: he had in mind the problems of philogenesis, including the restrictive condition posed by Weismann with the postulate of idioplasmatic continuity. In 1928, appointed by the California Institute of Technology, Morgan left New York for Pasadena, but the previous year one of his pupils, Hermann J. Muller (1890-1967), had publicised the discovery that X rays increased the frequency of mutations in an article that he had published in *Science*.[17] Mutations in the hereditary endowment had already been identified by this botanist, one of the discoverers of the essays written by Mendel of 1866 and 1869. On a plant from America, *Oenothera lamarckiana*, taken from botanical gardens developed in the environment, he found individual specimens that had an accentuated variability in size, leaf colour and colouration, and he considered each one of these variations a 'mutation'. This was the term that de Vries chose for the title of the work in two volumes that has already been referred to in this paper, namely *The Theory of Mutation*, which was to constitute the necessary complement to Darwin's *On the Origin of Species*. The current opinion of the time was that species slowly transformed into other different species. Mutationism, on the other hand, argued that new species and varieties derived from pre-existent forms through brusque jumps. Darwin had been a gradualist although he had also observed the existence of drastic variations which he termed 'sports'. In humorous fashion his friend Thomas H. Huxley reproached Darwin for shouldering a difficulty that was not necessary by accepting the idea that '*Natura non facit saltum*'. The experimental results achieved by Muller made possible a return to the parcelling variation of the gene system, but the conceptual distance between micro-evolution and macro-evolution had still to be bridged in a similar way: this would be done without recourse to 'selection' together with sexual reproduction seen as an instrument of recombination. Once again biologists found that they had to pass down the theoretical pathway of Weismann who had dedicated a specific essay in 1886 to the selective function of sexuality. This was three years after his work on the continuity of the germinal plasma.[18]

At the end of the 1930s genetics built a bridge between the two dominant biological paradigms – cellularism and 'evolution'. This last term had prevailed over 'descendance' because of the replacement of German by French and English as the dominant languages of science. The works that brought together the results and problems in this field were *Genetics and the Origin of Species*[19] by Theodosius Dobzhansky (1900-1975), with editions in 1937, 1941 and 1951 and republished in 1957, and *Evolution. The Modern Synthesis* by Julian Sorell Huxley (1887-1975), with editions in 1942 and 1963.[20] In the work by Dobzhansky, mutations and sexual reproduction could generate an unlimited variety of genotypes but reference to chance was held to be unjustified. It was argued that each mutation had a determined probability, took place separately from its utility, and the Mendelian changes in populations were 'everything but automatic results of fortunate throws of genetic dice or even of environmental requests…the evolutionary process can be described as creative'. Dobzhansky had gone back over the academic itinerary of Morgan from Caltech to Columbia, assuring this prestigious American university the merit of further programmes of research that would find a home and resources in that centre of learning. This step was one of the few where there would arise a prediction as to a future crisis for genes, genetics, evolution and selection. Even Morgan had observed, during his Nobel prize acceptance speech of 1933, that there was no agreement amongst geneticists as to whether genes should be considered real or a matter of convention. In the biologist Huxley, on the other hand, we encounter trust in a multidisciplinary synthesis as regards genetics with the emergence of the concept of 'population' and with the support of two new disciplines – ecology and statistics. Within these limits new developments certainly became accentuated but at the high cost of losing sight of the substance of the problem raised by biological heredity. The gene was a spatial entity in the structure of the genome. However, the gene was not alone: in the human genetic inheritance tens of thousands could be counted and the idea that flowered here and there at the beginning of the twentieth century, of correlating the genes and chromosomes one by one, ended up by appearing ingenuous to a point that now provokes amusement. Each one of the twenty-six chromosomes of *Homo sapiens sapiens* would show that it was the carrier of hundreds of gene units. What unified them within the matrix of the organism, not least because, preceding the future, it was shown that individual organs and functions depended on centres of gene control located in different chromosomes? The 'new synthesis' which Huxley put in the title of the volume cited above referred to an unprecedented relationship between disciplinary paradigms in order to explain the controversial problem of evolution, but it neglected the point of departure and limited itself to observing that the role of genetic entities was a subject that had by now passed into the hands of macro-molecular chemistry, with the

elimination of an old terminology in which were rooted terms such as 'protoplasm', 'trophoplasm', 'idioplasm' and yet others, which were regarded by the most informed authorities of the time as mere provisional appellations. Amongst those authors that have been cited, who, indeed, had the merit of concluding a fifty-year old pathway followed by genetics from Hertwig and von Beneden through Mendel and Morgan until the neo-Darwinains populationists (Ronald A. Fischer (1870-1962) of London, Sewall Wright (1889-1988) of Chicago and John B.S. Haldane (1892-1964) of London), it was Dobzhansky who perceived the need for a substantial advance and renewal of knowledge in this field. In the meantime Europe had retaken the initiative side by side with the United States of America with the John Innes Institute of Cambridge, the Kaiser Wilhelm Institut of Berlin, and the Institut de Biologie physicochimique of Paris. Morgan was still alive and dissatisfaction was spreading about formal genetics, a discipline attributed to him.

There was an attempt to find in chemistry what morphology could not provide. A hope was opened up by the micro-biologists of the Rockefeller Institute of New York, where the team of Oswald T. Avery (1877-1955), with Colin M. MacLeod and Maclyn McCarty, was working on pneumococci and acquiring the proof that bacterial virulence can be transmitted from one strain to another and become hereditary by a 'transforming principle' represented by deoxyribonucleic acid – DNA. Avery had published on this in the *Journal of Experimental Medicine* in 1944.[21] Dobzhansky, taking note of new post-Morgan genetics in the third edition of his work, observed that the power of transformation of the new substance was maintained even in extreme dilutions. The parallel but autonomous path of research on pneumococci had led on to research on bacterial viruses by the phage group which had been created at Caltech in Pasadena around Max Delbrück (1906-1981), with the participation of Salvador Luria and Alfred Herschey. Delbrück demonstrated that the ultramicroscopic particles that make up phages reproduce themselves in great numbers in a very short space of time. Luria placed his pupil James Watson, one of the future discoverers of the double helix, in this group in 1953.

To summarise: the 1940s had made chemistry enter the paradigm of hereditary processes with the identification of the nature but not yet the structure of the substances involved in those processes, and, at a distance of some decades, with the consolidation of a relationship between two contemporaries who had now known about each other: the botanist Mendel and the pathologist Johann F. Miescher (1811-1887) of Basilea, the discoverer of the acidic substance contained in the cell nuclei. In the work mentioned above by Avery, the DNA of the bacterial cell was defined as being 'functionally active' – it still had to be made clear what its function was in relation to the gene. George Baedle and Edward Tatum, between 1943 and 1945, had formulated the hypothesis that the beginning of the gene was to do with enzymes. But was DNA to be identified with the gene, and in that case it would come to form a part of this the hypothesis about the role of enzymes (which indeed was shared by many researchers of the time), or was it instead a gene-changing agent which had in the gene material its specific terrain of choice? The experiments of Delbrück with phages bore upon this question, in parallel with the experiments carried out by Avery on pneumococci – the high speed of the conversion of one strain into another excluded reference to a process of chance mutation and then subsequent selection. Erwin Chargaff (1905-2002) and his team at Columbia University made a major contribution to decoding, above all at a structural level, nucleic acids. 'An enormous outpouring of interest' in DNA had arisen. Two classes of nucleic acids were described – DNA and RNA – and their constituents had been identified: purine, pyramidine, pentose and inorganic acid. In two typical nucleic acids, DNA from salmon sperm and RNA from yeast, only one of the pyramidines varies, respectively represented by the thymid and the uracil, and where at 2-deisossis-D ribose of the DNA there is a substitution by D-ribose of the RNA. Chargaff would later refer to these experiments on life with words of exemplary insight: 'Yet there always remains the fact that we have destroyed an incredibly refined scaffolding; that we have interfered with an order whose level is unfathomable; and that, by the very fact of separating the components of cells we have destroyed their entelechial connection'.[22] With the merely structural hypothesis of the 'tetranucleotide', by which the pyrine and pyramidine of the DNA could have repeated itself nth. times in the (AGCT) form, deoxyribonucleic acid took on the role of an agent in the non-oral communication of 'biological information'.

But in the 1940s, a decade which witnessed the entrance into the paradigm of macro-molecular chemistry, the helix configuration of the composite took on a specific relevance. On 25 April 1953 a brief essay on 'The Molecular Structure of Nucleic Acids' by James D. Watson (1928-) and Francis Crick (1916-2004) was published in the journal *Nature*. It contained a portrayal of the double helix 'which immediately suggested a possible copying mechanism for genetic material', as the authors theselves wrote.[23] At what stage had the 'theory of the gene', to return to the phrase used by Morgan, now arrived? And should there or should there not be a theory of life behind that gene that was different from it? A contradictory approach emerged amongst biologists. Beneath the double helix there was a broad margin of real situations to be studied and defined. But DNA, in the collective mind, was by now identified with life, and genetics was the new and updated name of biology. And to such an extent that a terminology began to be used that was extraneous to the recent lexicon of biology and derived from a paradigm that was undergoing rapid advance within a context of uncontested authoritativeness – the theory of information. This argued that information was neither matter nor space but could instead be identified with the border between the two highest concepts of philoso-

phy and science: the concept of 'nature' and the concept of 'being'. If there was a compendium of information about life in the gene, the terminological transition from 'genetics' to 'genomics' was justified, together with the referred to matching of the genomic and biological paradigms.

The advances of genomics in the understanding of the synthesis of proteins in the three decades after Watson and Crick, or rather the four decades after Avery, gave form and substance to developments of unforeseen extension. RNA, from being a transmitter of the stereo-chemical message from DNA to the proteins, acquired an autonomous relevance as an original replicator, as a well as an original transmitter of the genomic message, in the history of living nature. The mapping of the human genome at the end of the twentieth century concealed this background fact, able to speak above all to the minds, the consciences and the people who felt that they carry within themselves the secret of the origins of the world. And such a secret is not hidden in the gene but in life, which has recently seemed to reacquire an ontological and logical priority. The return to the priority of living-life over genome-gene is also reflected onto the past, with a reassessment of the meaning of the cellular paradigm and the defining requirement that is implicit in it compared to evolution as the matrix of evolutionism. One after the other the other theoretical positions based upon the gene-genetics-genome trajectory fell by the wayside. For the geneticist William Gelbat 'we have perhaps reached the point when the use of the term 'gene'…could hinder our knowledge':[24] differently from chromosomes, genes are concepts more than material objects. Pathologies connected with an individual gene disease such as that of Tay Sachs's disease, Huntingdon's chorea, cystic fibrosis, thalassemia, or phenylketonuria, are different from others and these last are the majority because more than one gene is involved: cardiovascular diseases, strokes, and diabetes. The molecular geneticist of Oxford, David J. Weatherall, has well brought out the impossibility of departing from the various mechanisms of regulation within which a single gene can be transferred. The human genome project, observes Evelyn Fox Keller, the historian of science at MIT in Boston, has disappointed those who hoped that knowledge about the sequences involved would be sufficient to understand an organism, but it has been valuable because it has outlined a more realistic path by which to achieve an understanding of the workings of organisms.[25] There has emerged the crisis of the gene model – the enzyme, for that matter, is not of recent origins and goes back to the division of genes into 'structural' and 'regulatory' genes where the second activate and regulate the first which are responsible for the transcriptions at the level of the proteins.[26] The 'operon' model has come into being where it is held that within it are present all the factors which, co-ordinated by regulatory genes, work to achieve protein synthesis. But these are elements that are often distant from the codifying sequences. The stability of the structure of genes turns out to be not a point of departure but the final outcome of a hypercomplex process, whereas the replication of DNA implies the intervention of many different proteins with a process of very great complexity and amazing precision. The entelechial fruit of life and the living, cited, as has been observed in this paper, by Chargaff, seems to reemerge as a primary and undeniable evidence during the 'dream of the human genome', to use the phrase of the Harvard University geneticist Richard C. Lewontin,[27] but without his apparent sarcasm. That dream should not be forgotten, as is usually the case with the oneiric experience, but subjected to a lucid reflection that re-examines it and in a practical way places in within a different philosophy of nature.

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Notes

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DARÍO CASTRILLON HOYOS

2. Human Genetics in the Light of the Word of God

My task is to throw light on the subject of 'human genetics' in the light of the Word of God. On a first reading, it appears that nothing is to be found about genetics in Holy Scripture, and by genetics I mean here the biological science that studies the phenomena of heredity and variations in animal species.[1] It is certainly the case that there is no scientific intention to be found in the Word of God. The truths contained in Holy Scripture are not scientific propositions in the strict sense of the term, that is to say they are not theoretical empirical statements: they contain theological truths and theology is in itself a science. The Word of God transmits revealed truths for our salvation. 'The books of Holy Scripture teach with certainty, faithfully and without error, the truth that God, for our salvation, wanted to be communicated in Holy Scripture'.[2] Specifically for this reason, in Holy Scripture we discover the mystery of God and His design of love in relation to the Creation. This theological richness illuminates and clarifies the foundations of *genetics*.

On the other hand, the *genome* and *genetics* are in their own way also a *way in which God reveals Himself*. This is because they bear within themselves a wonderful and fascinating message that God 'wrote' for man in the Creation. The message of the love of God to be found in Genesis and the message of love of God that we discover in *genetics* come from God himself. For this reason, the first book of Holy Scripture offers us wonderful lessons of theology that serve to illustrate and enrich the science of geneticists just as genetics shows us the impress of God in the Creation thereby completing the work of theologians. The connections are many in number and in this paper I want to choose only some fundamental lessons where *Genesis illuminates genetics* and *genetics explains Genesis*.

1. The *first lesson* is that *Adam*, the son of Earth – this is the meaning of his name in Hebrew – *became a man solely through the action of God*: 'then the Lord God formed man of dust from the ground, and breathed into his nostrils the breath of life; and man became a living being'.[3]

God is the cause of man; his *Supreme Cause*. Every human being has a *human cause* and a *divine cause* at his or her origin. Genetic information in itself cannot be the cause of a human being if we accept that a human being is a spiritual being endowed with reason and free will. The spiritual soul is not present in genetics but is created individually by God. The soul, like the genome, can never be repeated and is *created* and not *generated*. The genome, on the other hand, is created. Genetics explains the human being but does not *explain everything in* the human being; it does not explain the *cause* of a human being but indicates his or her *origins*.

It is true that the 'modern knowledge of molecular biology allows us to observe that every living being has a genome specific to its species, and this is precisely what defines it as a member of that species and not of another'.[4] But however much the genome teaches us about membership of the human species, it does not in itself provide the condition for the person.[5] It is sufficient to observe how many cells of our bodies, separated from our bodies as well, although they possess a complete genetic endowment are nonetheless not persons. The genome is an *identity document* but the *ultimate reason for such identity* is to be looked for elsewhere, namely the Creator of the genome.

God is the author of human life, of every human life. Life is a gift of the love of God to man. 'Why is life a good?', the question recurs throughout the Bible and as early as the first pages of the Bible we find an effective and admirable answer. The life that God gives to man is original and different from that of the other living creatures because man, although he comes from the dust of the earth,[6] is a manifestation of God in the world, a sign of His presence, the splendour of his glory.[7] This is what St. Ireneus of Lyons wanted to emphasise in his famous definition: 'the glory of God is living man'.[8] Man has been given a very high dignity which has its specific roots in the intimate tie that unites him to his Creator: in man is reflected the very reality of God.[9]

2. And here we have the *second lesson* that is offered to us by Holy Scripture: the genome is not a human being. It *identifies* a human being but it does not *define* a human being. In a human being there is an intelligence, a responsibility and a freedom that are not the outcome of the organic world. They belong, rather, to the world of the spirit. A human being is much more than a genome. It is the spiritual soul that bestows dignity on the genome, and not the opposite. The Universal Declaration on the Human Genome and Human Rights of UNESCO states that the 'human genome forms the basis of the fundamental unity of all the members of the human family and of the recognition of its dignity and intrinsic diversities'.[10] As formulated, the text seems to mean that a human being has in the genome the foundation of

his or her own dignity. In reality it is the dignity of man and the unity of the human family that confers value on the *human genome* and requires this genome to be protected in a special way.

In accepting the biological concept of *species*, the question can be formulated in the following way: what characterises the individuals that belong to the human species and differentiates them from the members of other animal species? One might think that the answer is specifically the genome but the experimental data tell us that the genetic information of both the human species and other species have over 90% of their genes in common and the chromosome organisation matches to the level of 99% or beyond. Is it, therefore, what is to be found in the DNA[11] of the human species that bestows upon that species its singularity? It is certainly the case that today it appears to be impossible to manage to identify, to isolate and to characterise the genetic information within the *human genome* that bestows upon us the category of human beings. In a debate on the Human Genome Project,[12] Dr. J. Craig Venter alluded to the interest that a parallel implementation of a Chimpanzee Genome Project could have, a project that would allow a comparison of the sequence of the genome of man with the sequence of the genome of chimpanzees and perhaps allow the discovery of some relevant differences between the respective DNAs.

It appears, instead, that what determines a human being at a genetic level, and differentiates him from every other animal species, is expressed in his *behaviour*. In his or her behaviour a human being expresses capacities that differentiate him or her from other animal species. The capacities that are developed go well beyond any genetic information. In a human being, in fact, there are the capacities for reflection, for decision taking, and for reasoning that make the human being unique.

For this reason one may say that in a human being the genome is a *mark of identity* but it is not the identity. In genetics we find the image and likeness of God that are present in every human being. '*The vocation to love* is what makes man the authentic image of God: he becomes more similar to God the more he becomes *someone who loves*'.[13]

'Man, in fact, is a soul that expresses itself in a body and a body that is vivified by an immortal spirit. The body of a man or of a woman, therefore, so to speak, also has a theological character and is not simply a body, and what is biological in man is not only biological but is an expression and completion of our humanity'.[14]

The subject is not the genome but the person. It is the personal 'I' which sustains the genome, and not the opposite. The human soul, which is spiritual, gives life to the genome and confers on the human being his or her specific faculties: intelligence and free will. For this reason, *Jesus* Christ, real God, *is a real man* not only because he has the *human genome* but also because *he takes on human nature*. Christ is human because of his genetics but he is also and above all else human because he has a spiritual soul which makes him capable of loving, capable of thinking, and capable of deciding in a free way.

3. The *third lesson* is that *a human being is a being who is profoundly dependent upon God*. God is the origin of human life but He is also the model to which it is directed. In Genesis, of all the created beings, only man receives a commandment directly from the Lord: 'be fruitful and multiply'.[15] The task appears as a gesture of love full of trust towards man: 'be fruitful and multiply, and fill the earth and subdue it; and have dominion over the fish of the air and over the birds of the air and over every living thing that moves upon the earth'.[16] This is like a sheet of instructions on the Creation: 'Behold, I have given you every plant yielding seed which is upon the face of the earth, and every tree with seed in its fruit; you shall have them for food. And to every beast of the earth, and to every bird of the air, and to everything that creeps on the earth, everything that has the breath of life, I have given every green plant for food'.[17] God places His work in the hands of the human being and at the same time invites him to steward it as something created for his welfare. The way in which He says this, addressing a plurality of persons, further emphasises that reference is being made to the human species, to all human beings.

Why does the Lord do this? Why is the human being the only creature to receive explicit instructions from God? Why do the other beings not receive such instructions? In these beings the instructions are written into their instincts, they are pre-determined, but the human being is the only being who can understand the instructions of God and co-operate actively with Him, in an aware and free way. This is the profound difference. Life, every life, has a long history; each individual of every animal species has a very precise beginning: the moment

of its conception. A human being, however, is the only being that from this beginning begins a task of self-construction and a task that involves the responsible use of the rest of the Creation. Each human being, like every animal, from the beginning of his or her life, from his or her first cell, begins to make himself or herself, to construct himself or herself. However he or she is the only being to proceed along this path in a conscious way as a task for which he or she is responsible.

'We see here a clear affirmation of the primacy of man over things;

these are made subject to him and entrusted to his responsible care, whereas for no reason can he be made subject to other men and almost reduced to the level of a thing. In the biblical narrative, the difference between man and other creatures is shown above all by the fact that only the creation of man is presented as the result of a special decision on the part of God, a deliberation to establish a particular and specific bond with the Creator: 'Let us make man in our image, after our likeness'.[18] The life which God offers to man is a gift by which God shares something of himself with his creature. Israel would ponder at length the meaning of this particular bond between man and God. The Book of Sirach too recognises that God, in creating human beings, 'endowed them with strength like his own, and made them in his own image'.[19] The biblical author sees as part of this image not only man's dominion over the world but also those spiritual faculties which are distinctively human, such as reason, discernment between good and evil, and free will: 'He filled them with knowledge and understanding, and showed them good and evil'.[20] The ability to attain truth and freedom are human prerogatives inasmuch as man is created in the image of his Creator, God who is true and just.[21] Man alone, among all visible creatures, is 'capable of knowing and loving his Creator'.[22] The life which God bestows upon man is much more than mere existence in time. It is a drive towards fullness of life; it is the seed of an existence which transcends the very limits of time: 'For God created man for incorruption, and made him in the image of his own eternity''.[23, 24]

4. The *fourth lesson refers to human nature*. It is true that the modernist philosophical wish to 'free' nature from the weight of God leads to a losing sight of the reality itself of nature, including the nature of man, by reducing it to a set of functions which can be disposed of according to one's own tastes so as construct a supposedly better world and a supposedly happier mankind. Instead, one destroys the design of the Creator and at the same time the truth of our nature.

Today we know that the *genetic map* shows that human beings are like twins. This is because of the three million characters that we carry written into our chromosomes only a few thousand actually vary. In other words, over 99.9% of the genetic map of every individual is the same. The genetic information contained in each cell would occupy about a hundred thousand pages of a periodical journal. About 99,900 pages would be the same for all human beings. The remaining hundred are those that make up our statute, our metabolism and the colour of our skin. For this reason the discoveries of Craig Venter, Francis Collins and the other researchers of the Human Genome Project, contextualise categories that until a short time ago were considered social myths, such as, for example, the concept of race. There is no genetic code that distinguishes Slavs from bushmen. The differences and the similarities between the two races are as weak as those between two people born in the same village.[25]

All human beings have the same nature, the same dignity. The differences between them are only contingent. Human nature guides people towards a form of behaviour. This is a nature that cannot be reduced, as has been observed, to a biological dimension: it goes beyond this. A human being is distinguished from the other beings of the creation by these spiritual capacities that are specific to his or her nature which rise above the material plane: the capacity to love, freedom of choice, the capacity to understand and to follow the mandate received from God. And this nature marks out an ethical direction in the human being who is the only being that is co-responsible with God for the Creation.

5. Having come to this point we can now engage in a shift in perspective and begin with genetics so as to discover new elements that are of use to us in appreciating the marvellous identity and dignity of human beings.

Thirty-five years ago, in the United States of America, the sentence of the Supreme Court in the case denominated *Roe versus Wade*[26] stated that given that we do not know the moment when human life begins we are free to decide as we wish. Since then science has achieved astonishing advances. Today we know that *life* has a very long history; it was transmitted millennia of years ago to mankind; however, each one of us has a precise moment of beginning, which is that moment when all the necessary and sufficient genetic information comes together in a cell, the fertilised ovule. That moment is the moment of fertilisation and there is not the least doubt about this.[27]

We may say of an embryo that is a week old that 'it is a man' or 'it is a woman'. It is beyond imagination that legislators, coldly recognising that this embryo that is a week old is a baby boy or a baby girl, would not want to recognise at the same time that it is a human person.[28]

Life is written in a fantastically reduced language. When the 'Roe versus Wade' verdict was given, although it was known that within the first cell genetic information was to be found, nobody could read it and nobody was able to foresee the way in which it would express itself so as to become a living being who could say to us: 'I am a human being'. Today, we know that life is very similar to what takes place on a magnetic tape on which music has been recorded. On the tape there are no notes. In the recorder there are no musicians; nor are there musical instruments. However, because the information was codified when it was received from a microphone and then transmitted onto the tape, the machine can read it, give impulses to the speakers, and so what is reproduced are not the musicians or the notes of the musical score. What is transmitted, if you listen to the 'Little Serenade', is the genius of Mozart.[29]

We are able to recognise beyond any doubt who is the biological father of the embryo. Society, rather than seeing the baby as a criminal to be eliminated through abortion, must recognise it as a human being. If we know the parents, a human being with an unworthy father must be the concern and not the victim of a nation.[30]

From these data one can deduce a *third lesson*: God granted to human beings an intellectual capacity that is of use to them in discovering God's traces in the Creation, and es-

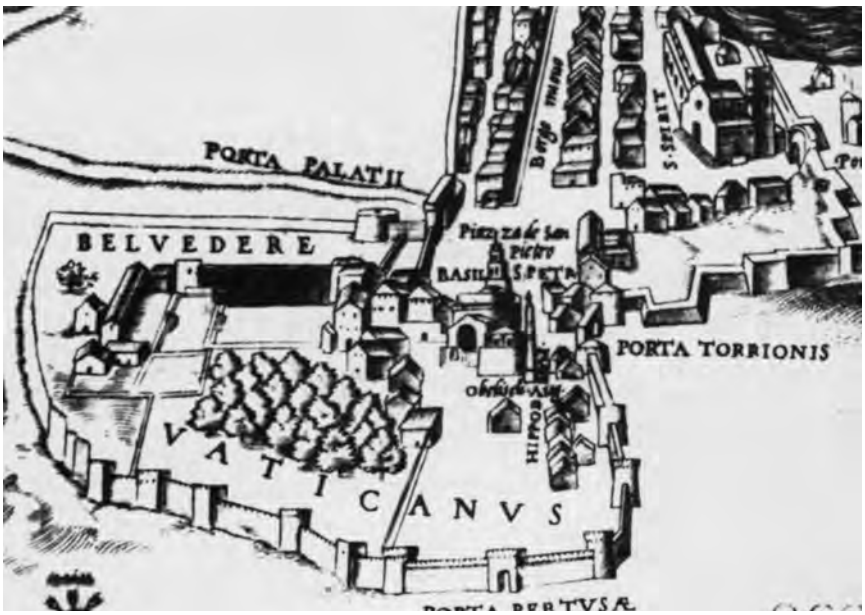
pecially in themselves, so as to rationalise from experience the moral laws that the Lord gave them through Revelation. In this one once again discovers the image and the likeness of God[31] that exist in human beings, and this is a central theme of Genesis. However, a human being can act against such evidence.

6. The *sixth lesson* emphasises the importance acquired by *sexual differentiation* and *complementariness* in the plan of God. The text of Holy Scripture in the two accounts of the creation of man speaks about a sexual complementariness: 'male and female he made them'.[32] This *sexual differentiation* profoundly marks a human being and genetics reveals to us that this very difference is written into *every cell of the body* from the first moment of conception. Human nature bears the stamp of sexuality as a sign of complementariness, as a domain of love. In this way, God writes into the humanity of a man and a woman their vocation and as a result the capacity and responsibility for *love* and *communion*.[33] Once again, what *Holy Scripture* teaches us we are also told by *genetics*.

Dr. Alec Jeffries, a distinguished specialist on DNA, discovered that the genetic message of the *spermatozoon* was emphasised in a way that was different to the genetic message transported by the *ovule*. When one studies something and one is reading a book very often one takes a pencil and underlines a sentence that one thinks one should remember because it is very important. And at times one places an 'X' on another passage because it is not needed right away. This is exactly what nature does with the totality of the genetic message.[34]

At the beginning of our lives we have two metres 'of tape', and the quantity of letters written on these two metres is five times greater than the Encyclopaedia Britannica. To put it another way: to imprint the name of all the existing bases of our genetic code we would need five series of volumes of the size of the Encyclopaedia Britannica. We can thus understand why it is very prudent of nature to underline certain sentences. This is because they have to be deciphered immediately by the first cell. And why nature places an 'X' on others – they will be used much later in life. The cell cannot do everything at the same time – it has to begin with one part.[35]

In *men* a part of the message is underlined and in *women* another, different, part, is underlined. What has been underlined in the male message says to the first cell how to construct the membrane that will protect the baby and how to construct the placenta that will take the supplies of blood of the mother. Thus, in fact, the man in the first cell has the duty of procuring nourishment and building the dwelling, constructing the hut and going hunting. In contrary fashion, the female message is on how to form different parts which, once they have been assembled, will form a baby. It is truly extraordinary that the division of tasks that we find in adults is already written into the reduced language of genetics in the first cell of a millimetre and a half in length which is the epitome, the compendium, the diminution to the smallest expression, of the human person.[36]



The sexual differentiation that the genome demonstrates to us is at one and the same time both *indicative* and *normative*. It is a genetic datum that marks every cell of a human being. A human being receives this sexual differentiation as a gift that God makes to him or her as a function of his or her vocation to the love of complementariness. Indeed, 'God created man in His image and likeness:[37] in calling him into existence for love, He called him at the same to time to love. God is love[38] and lives in Himself a mystery of personal communion of love. In creating humanity in His image and constantly conserving it in being, God writes into the humanity of man and woman the vocation to, and thus also the capacity and responsibility for, love and communion.[39] Love is, therefore, the fundamental and native vocation of every human being. As an embodied spirit, that is to say a soul that expresses itself in a body and a body informed with an immortal spirit, man is called to love in this unified totality that is his. Love embraces also the human body and the body is made a participant in this spiritual love.[40] In the plan of God there is a sexual differentiation that directed towards the love of mutual self-giving in complementariness.

Contemporary voluntarism suggests and allows the possibility of a so-called 'sex change' in order to redirect a human being in line with his own sexual tendencies. This change, however, does not manage to modify the genetic code of each cell which bears written within it sexual differentiation. One is dealing here with a change of the *gonadic, morphological, phenotype* sex in order to adapt to the *psychic sex*, but one cannot change the genetic sex, that which *characterises*

human sexuality understood as an essential characteristic of the person and not merely an accidental activity. It is true that human sexuality is much more than genetic, yet one must respect what nature has written into genetics.

7. The *seventh lesson* teaches us something about the relationship between genetics and predetermination and this lesson is that the genome does not predetermine a human being but marks many of his or her somatic characteristics. Craig Venter, the founder of Celera Genomics, the leading private company in integrated genetic research belonging to the Human Genome Project, draws the conclusion that 'the wonderful diversity of human beings derives not so much from the genetic code that is inscribed into our cells but in how our biological heredity relates to the environment'.[41] 'We do not have sufficient genes to justify the notion of biological determinism',[42] declares Craig Venter, who emphasises that it is highly improbable that there can exist specific genes that give rise to alcoholism, homosexuality or criminality.

If one can draw a conclusion from our knowledge of the genetic map it is that man is very little determined by his genes, given that a great diversity of forms of human behaviour sits in opposition to the extraordinary genetic similarity of each of their cells.

In advancing with the above deductions, Holy Scripture presents us with *Cain and Abel*, two very similar beings at the level of genetics but very different as regards their deepest choices, their relationship with the Creator.

Cain and Abel were almost equal from a genetic point of view but in the history of salvation they have remained located, if one can express the point in this way, in radically distinct categories: that of the good and upright man and that of the man who kills his own brother. Cain commits the crime of attacking human life. 'The question "What have you done",[43] which God addresses to Cain after he has killed his brother Abel, interprets the experience of every person: in the depths of his conscience man is always reminded of the inviolability of life – his own life and that of others – as something which does not belong to him, because it is the property and gift of God the Creator and Father'.[44] Why did Cain do this? Was it already in his genes?

The Greek philosophers had already discussed the question of the primacy of *nature* or *culture* in the formation of personality. Recent genetic discoveries reaffirm the importance of culture. An individual is born with certain biological conditionings but it is the family, school and the environment that directs him or her in the choice of a pathway between the thousands of possibilities offered by existence, and this choice of a pathway is in itself free even though it can be very influenced. For this reason, genes are responsible only for the fact that we are fair or dark, and not for our failures or our errors, just as in the same way they do not explain success or genius. The most likely thing is that in the genes of Miguel Cervantes, Dante Alighieri, William Shakespeare, Leonardo Da Vinci, Michelangelo Buonarroti or Wolfgang Mozart there was nothing that differentiated them from their progenitors or their brothers or sisters. This demonstrates that in a human being above the genes there is above all else personal taste and the freedom to choose.

The studies on the *human genome* tell us that even though they increase our knowledge of human beings, human beings continue to be a *great mystery*. The genes of a saint can be the same as those of a criminal. The difference between the behaviour of the former and the latter lies in the stimuli that they have received from without and above all else in their own capacity *to choose freely*. This is something that appears sadly in Genesis, the drama of a human being who kills his own blood brother, the son of his own parents, who was brought up in the same environment and created in the same way. And this inheritance we still bring with us from birth.

8. After contemplating the inheritance of sin within human beings, the *eighth lesson* fills us with hope in discovering that the *human genome* is the *mark of a lineage destined to defeat evil*. The so-called *protoevangelio* of Genesis presents us with a prophecy that refers to the whole of human descent born from Eve: 'I will put enmity between you and the woman, and between your seed and her seed; he shall bruise your head, and you shall bruise his heel'.[45] This is the first announcement of the *redemption*. It marks a clear enmity between the serpent and mankind that will last until the time when the human lineage bruises the head of the serpent. Unfortunately, the Greek translation has the last sentence begin with a male pronoun which appears to attribute victory not to the lineage of woman in general but to a man descended from her, but this is not what is said in the Hebrew text, which clearly indicates that the victory will be of the whole of the descent. In Latin this has been interpreted with the famous '*ipsa conteneret caput tuum*',[46] which the Fathers always refer to Mary. Mary is she who as Mother generates the new humanity that has overcome evil, which has defeated evil. The woman is the centre and the head of saved humanity. Mary is the new Eve because she is the Mother of the living, *the living in grace*; not only through *biological life* but also through the life of grace which is the presence of divine life in the soul.

Mary, the descendant of *Eve* in the genetic lineage, is the first of a new *spiritual lineage* that is invited to be born once again in holiness. To her we are called by eternity.

H. Em. Cardinal DARIO CASTRILLÓN HOYOS
Prefect of the Congregation for the Clergy, the Holy See

Notes

[1] Contemporary *genetics* can be divided into *subject* and *methods* in its various branches: formal and cytological genetics, which studies the laws of the transmission of hereditary characteristics and the cytological mechanisms that are responsible for this; *physiological* genetics, which investigates the ways genes act and the physiological and biochemical processes by which they express themselves; and the genetics *of populations* and the genetics *of evolution*, which study the relationships and the distribution of genes and their variations within populations.

[2] Second Vatican Council, Dogmatic Constitution *Dei Verbum*, 11.

[3] Gen 2:7.

[4] Pilar Calva, 'Genoma humano', in J. M. Septién (ed.), *El aborto. Ética, verdad y justicia* (Diana, Mexico, 2003), p. 34.

[5] Cf. M. Crespo, *Menschenwürde: Metaphysik und Ethik* (Universitätsverlag C. Winter, Heidelberg, 1998); J. F. Crosby, *The Selfhood of the Human Person* (The Catholic University of America Press, Washington, 1996); R. Guerra, *Afirmar a la persona por s misma* (CNDH, Mexico 2003); R. Guerra, *Volver a la persona* (Caparrós, Madrid, 2002); J. Seifert, *Essere e Persona* (Vita e Pensiero, Milan, 1983); M. Serreti, *Conoscenza di sè e trascendenza* (ISTRA-CSEO Saggi, Bologna 1984); R. Spaemann, *Personas. Acerca de la distinción entre "algo" y "alguien"* (EUNSA, Pamplona, 2000); K. Wojtyla, *Persona e Atto* (Bompiani, Milan, 2001).

[6] Cf. Gen 2:7; 3:19; Job 34:15; Ps 103/102:14; 104/103:29.

[7] Cf. Gen 1:26-27; Ps 8:6.

[8] '*Gloria Dei vivens homo*': *Ad. Haer.*, IV, 20, 7.

[9] John Paul II, Encyclical Letter *Evangelium vitae*, n. 34.

[10] UNESCO, Universal Declaration on the Human Genome and Human Rights, Paris, 11 November 1997, art. 1.

[11] Abbrevition for Deoxyrribonuleic Acid.

[12] Dr. Santiago Grisolía (ed.), *El Derecho ante el Proyecto Genoma Humano* (Bilbao, Spain, 1993).

[13] Benedict XVI, 'Address to the Ecclesial Congress of the Diocese of Rome',6 June 2005.

[14] Benedict XVI, 'Address to the Ecclesial Congress of the Diocese of Rome',6 June 2005.

[15] Cf. Gen 1:22.

[16] Gen 1:28.

[17] Gen 1:29-30.

[18] Gen 1:26.

[19] Sir 17:3.

[20] Sir 17:6.

[21] Cf. Deut 32:4.

[22] Second Vatican Council, Pastoral Constitution *Gaudium et spes*, n. 12.

[23] Wis 2:23.

[24] John paul, Encyclical Letter *Evangelium vitae*, n. 34.

[25] Cf. *Diario El Mundo*, Madrid, 12 February 2001, Opinión Editorial: 'El mapa del ser humano reafirma la libertad individual'.

[26] The verdict of the Roe vs. Wade case of 22 Janury 1973 legalised abortion in the United States of America.

[27] Cf. Jerome Lejeune, 'Discurso ante la Asamblea Legislativa del Estado de Louisiana (USA), 7 de junio de 1990', *All About Issues*, Vol 5, October 1991, pp. 17-20. Rights belong to the American Life League. Translated by Dr. Armando Cifuentes Ramírez, Cali, Colombia.

[28] Cf. Jerome Lejeune, 'Discurso ante la Asamblea Legislativa del Estado de Louisiana (USA), 7 de junio de 1990', *All About Issues*, Vol 5, October 1991, pp. 17-20. Rights belong to the American Life League. Translated by Dr. Armando Cifuentes Ramírez, Cali, Colombia.

[29] Cf. Jerome Lejeune, 'Discurso ante la Asamblea Legislativa del Estado de Louisiana (USA), 7 de junio de 1990', *All About Issues*, Vol 5, October 1991, pp. 17-20. Rights belong to the American Life League. Translated by Dr. Armando Cifuentes Ramírez, Cali, Colombia.

[30] Cf. Jerome Lejeune, 'Discurso ante la Asamblea Legislativa del Estado de Louisiana (USA), 7 de junio de 1990', *All About Issues*, Vol 5, October 1991, pp. 17-20. Rights belong to the American Life League. Translated by Dr. Armando Cifuentes Ramírez, Cali, Colombia.

[31] Cf. Gen 1:26.

[32] Gen 1:27.

[33] Cf. John Paul II, Post-Synodal Apostolic Exhortation *Familiaris Consortio*, n. 11; Cf. Second Vatican Council Pastoral Constitution *Gaudium et spes*, 12.

[34] Cf. Jerome Lejeune, 'Discurso ante la Asamblea Legislativa del Estado de Louisiana (USA), 7 de junio de 1990', *All About Issues*, Vol 5, October 1991, pp. 17-20. Rights belong to the American Life League. Translated by Dr. Armando Cifuentes Ramírez, Cali, Colombia.

[35] Cf. Jerome Lejeune, 'Discurso ante la Asamblea Legislativa del Estado de Louisiana (USA), 7 de junio de 1990', *All About Issues*, Vol 5, October 1991, pp. 17-20. Rights belong to the American Life League. Translated by Dr. Armando Cifuentes Ramírez, Cali, Colombia.

[36] Cf. Jerome Lejeune, 'Discurso ante la Asamblea Legislativa del Estado de Louisiana (USA), 7 de junio de 1990', *All About Issues*, Vol 5, October 1991, pp. 17-20. Rights belong to the American Life League. Translated by Dr. Armando Cifuentes Ramírez, Cali, Colombia.

[37] Cf. Gen 1:26 ss.

[38] Cf. 1 Jn 4:8.

[39] Second Vatican Council, Pastoral Constitution *Gaudium et spes*, n. 12.

[40] John Paul II, Post-Synodal Apostolic Exhortation *Familiaris Consortio*, n. 11.

[41] *Diario El Mundo*, Madrid, 12 February 2001, Opinión Editorial: 'El mapa del ser humano reafirma la libertad individual'.

[42] Cf. *Diario El Mundo*, Madrid, 12 February 2001, Opinión Editorial: 'El mapa del ser humano reafirma la libertad individual'.

[43] Gen 4:10.

[44] John Paul II, Encyclical Letter *Evangelium vitae*, n. 40.

[45] Gen 3:15.

[46] In the Latin edition of the Nea Vulgata, '*ipsa*' is replaced by '*ipsum*', thereby emphasising the referenc to the genetic lineage: '*Inimicitias ponam inter te et mulierem et semen tuum et semen illius; ipsum conteret caput tuum, et tu conteres calcaneum eius.*

PAUL LAURITZEN

3.The Ethics of Medical Genetics: The Challenge of Realizing the Potential of Genetic Medicine without Reducing Ourselves to Artifacts

It is a great honor, if somewhat daunting, to be here today among such a distinguished group of scholars. I am particularly humbled by the work of those who have addressed the "reality" of genetic science in our contemporary situation. The scientists who have dedicated their lives to service to others through exploring the therapeutic potential of genomic research deserve our gratitude and respect. My task, however, is somewhat different from that of most of the speakers who have come before me at this conference. My talk falls in the section of the conference on "Illumination," which is devoted to reflection on the spiritual and ethical dimensions of work on the human genome. Thus, although I believe that when genomic medicine is conducted responsibly it offers great hope for healing the sick and comforting the suffering, I see my charge as raising some of the moral dangers we face in pursuing a future of genomic medicine.

Let me begin by framing my comments in terms of two general qualifications. First, I want to reflect not merely on the ethical and spiritual dimensions of genetic research and medicine narrowly construed, but instead to place genetic research in a broader context of biotechnological research and regenerative medicine more generally. That is to say, I believe that in thinking about the ethical and spiritual implications of genomic medicine we need to attend to a whole range of issues related to embodiment, species boundaries, and human nature that are raised by recent developments in what Bruce Jennings has referred to as the "regime of biopower."[1] Second, although what I will say is, I believe, relevant for reflecting on this regime of biopower generally, my comments grow out of my experience in the American context. As you know, the peculiar American preoccupation with individual autonomy is often at odds with a concern for the common good and solidarity with the poor and the marginal in society. Thus, some of the concerns I will raise may be particularly acute in the United States, even though these concerns deserve general attention.

With these qualifications in mind, let me begin with a passage from C.S. Lewis's marvelous essay, "The Abolition of Man." Although this essay was originally published in 1947, its relevance to our topic is indisputable. Lewis writes: "The final stage is come when man by eugenics, by prenatal conditioning, and by an education and propaganda based on perfect applied psychology, has obtained full control over himself. *Human* nature will be the last part of nature to surrender to man.[2] When this happens, Lewis says, men will no longer be men; instead they will be artifacts. Humanity's conquest of nature will have "proved to be the abolition of man."

Lewis's concern about turning humans into artifacts sets the stage for the first theme I wish to explore, namely, the significance of the fact that the regime of biopower holds out the prospect of fundamentally changing the meaning of human embodiment by transforming the contours of human life in important ways.

To get a sense of the kind of issue related to changing the contours of human existence, consider the notion of a natural trajectory of human life. Although the concept of a life trajectory has played a role in some bioethics debates, genetic technologies pose a significant challenge to the very notion of such a trajectory and to conceptions of human nature in which a species-typical pattern of aging has normative significance. Consider, for example, how the Lutheran moral theologian, Gilbert Meilaender, uses the idea of a trajectory of human life to illustrate fundamental issues in bioethics.[3] According to Meilaender, two views of what it means to have a life and to be a person have been at war with each other within the field of bioethics over the past thirty years and these views underwrite sharply different positions on practically every moral issue we might confront in the field. On Meilaender's view, having a life means precisely that there is a trajectory that traces a "natural pattern" in embodied life that "moves through youth and adulthood toward old age and, finally, decline and death."[4] As he puts it, "to have a life is to be *terra animata*, a living body whose natural history has a trajectory."[5] Although Meilaender develops the notion of a natural trajectory of bodily life primarily to address the issue of euthanasia and not genetic technologies, his talk of "natural history," "natural pattern," and "natural trajectory" draws attention to one of the most significant questions raised by contemporary biomedical science: Will genomic research and related technologies change the very notion of a human life constrained by the natural aging process of embodied existence, and, if so, should such a change be resisted morally?

Meilaender does not take up this question explicitly, but I think there is little doubt that he would resist

any change that significantly alters the natural trajectory of embodied existence. Nor is he alone in this regard. Other members of President George W Bush's Council on Bioethics, most notably, Leon Kass and Francis Fukuyama, have also raised similar concerns.[6] Although those who oppose biotechnological interventions that may change the shape of the human life cycle are sometimes lumped together as "life cycle traditionalists," it is important to note that changing the trajectory of a life raises two distinct concerns.

The first is a more or less straightforward concern about the social consequences of altering the human life cycle and is nicely illustrated by Francis Fukuyama's discussion of the social implications of dramatically lengthening the human life span in his book, *Our Posthuman Future*. Suppose, he says, that regenerative medicine realizes its promise. Suppose that the average life span moves from 70 to 110 years or longer. What social dislocations can we expect? Among other consequences, Fukuyama writes, those 65 and older "will have a much more attenuated relationship to both family and work. They will be beyond reproductive years, with links primarily to ancestors and descendants." Those age 65-85 "may choose to work, but the obligation to work and the kinds of mandatory social ties that work engenders will be replaced largely by a host of elective occupations." Those 85 and older "will not reproduce, not work, and indeed will see a flow of resources and obligation moving one way: toward them."[7]

The second concern is often expressed in terms of a threat to human identity or what it means to be human, and although this concern frequently has a consequentialist cast, it comes in a largely non-consequentialist form as well. In my view, Walter Glannon has developed the most interesting form of the identity argument. According to Glannon, one direct consequence of significantly increasing the human life span would be to attenuate the relationship among past, present, and future mental states of a self and thus undermine the psychological grounds of personal identity. Because a sense of psychological connectedness between the present and the future is necessary to ground future-oriented desires, the inevitable erosion of a sense of connectedness that would come with a much longer life would, paradoxically, result in the extinction of the desire for a longer life. Without a reasonably strong sense of psychological connectedness to some future self, there would be little reason to take an interest in the potential projects of such a future person. Thus, even though there would be biological continuity between a present and distant future self, there would not be psychological continuity. As Glannon puts it, "there would be a divergence of our biology from our psychology."[8]

Strictly speaking, it would be more accurate to say that a new biology would result in a new psychology. And, in fact, such a formulation is more consistent with Glannon's analysis, one aspect of which involves examining the formation-storage-retrieval process by which the brain maintains the equilibrium between remembering and forgetting that is critical to psychological unity. Discussing the function of activator and blocker CREB (cyclic AMP response element binary protein), Glannon writes:

"The function of this protein suggests that the requisite unity between these states can hold only for a limited period of time. Anticipation cannot extend so far into the future that it undermines memory of the past. By the same token, there cannot be so much stored memory of past events that it comes at the expense of our ability to anticipate and plan for the future. A break in this equilibrium would... undermine our ability to sustain long-term projects by breaking the unity of forward- and backward-looking attitudes necessary to ground these projects".[9]

I hope that this passage makes clear why I recommend reformulating Glannon's maxim. It is not that increasing the life span causes psychology and biology to part company. Rather, the point is that changing the biology of human aging would profoundly change human psychology.

On one level, then, Glannon's concerns about using regenerative therapies to increase the human life span significantly is a consequentialist worry about the psychological effects on humans of disassociating the present from the distant past or remote future. For Glannon, we cannot rationally desire to lengthen the human life span dramatically because doing so would have disastrous consequences for our ability to undertake projects, accept responsibility for our past or future actions, or indeed, even care very much about "our" future.

Notice, however, that there is a corollary to our reformulated maxim. If a new biology gives rise to a new psychology, it also gives rise to a new ethics. Or to put the point negatively, a new biology threatens our existing ethical commitments. In fact, I think it is precisely a concern of this sort that animates the opposition of the life cycle traditionalists to various genetic technologies that might alter the trajectory of a human life. For example, when Leon Kass says that there are "many human goods that are inseparable from our aging bodies, from our living in time, and from the natural life cycle," he undoubtedly has this worry in mind.[10] It is also the concern raised by Francis Fukuyama's in his book, *Our Posthuman Future*. According to Fukuyama, there is an inextricable link between the concept of "nature" and any meaningful talk of human rights, and once we recognize the relationship between human rights and human nature, we see why even some secular ethicists are worried about moving toward a posthuman future. The fear is that biotechnology will cause us to lose our humanity in the sense that it may change the species-typical characteristics shared by all humans as humans. If that happens, and if human rights are, for many, tied more or less directly to a conception of human nature, then biotechnology threatens the very basis of human morality as we know it.

The second theme I wish to explore with you today can be introduced by quoting from a letter that Pope John Paul II wrote to the Apostolic Nuncio in Poland on the occasion of the international conference in 2002 entitled, "Conflict of Interest and its Significance in Science and Medicine."[11] As always, the pope was concerned about issues of social justice, and in relation to the themes of the conference, he was concerned especially

about how profits and patient care do not always align. "While it is certainly proper for a firm in the field of biomedical or pharmaceutical research to seek an appropriate return on investment," the Pope wrote, "it sometimes happens that overriding financial interests prompt decisions and products which are contrary to truly human values and to the demands of justice, demands which cannot be separated from the very aim of research. As a result, a conflict can arise between economic interests on the one hand and, on the other, medicine and health care. Research must be pursued for the good of all, including those without means." When profits are put before people, the pope says, "science is deprived of its epistemological character, according to which its primary goal is the discovery of truth. The risk is that when research takes a utilitarian turn, its speculative dimension, which is the inner dynamic of man's intellectual journey, will be diminished or stifled."

Both the conference on conflicts of interest in science and medicine and the pope's letter highlight the second set of concerns that I want to discuss today and which can go under the rubric, problems with commodifying biomedical research and health care. The issue of the commodification of health care is an enormous topic and one on which Catholic writers have made important contributions. For example, one of the best discussions of commodification in the bioethics literature in English is a collection of essays that appeared in a focus issue of the *Journal of Medicine and Philosophy* edited by M. Cathleen Kaveny, a Catholic theologian and legal scholar at Notre Dame University.[12] And one of the best essays in that issue is by the distinguished Catholic physician and bioethicist Edmund Pellegrino, who was recently appointed to chair President Bush's Council on Bioethics. Pellegrino focuses on the threat that conceptualizing health care in market terms does to the physician-patient relationship. He rightly notes that when doctors and patients interact as buyers and sellers in a market, the physician-patient relationship almost always suffers: communication breaks down, continuity of care is difficult, and suspicion replaces trust. There are other problems as well, particularly involving social justice concerns. Here is how Pellegrino makes this point:

There is no room in a free market for the non-player, the uninsured, the uninsurable. The special needs of the chronically ill, the disabled, infirm, aged, and the emotionally distressed are no longer valid claims to special attention. Rather, they are the occasion for higher premiums, more deductibles, or exclusion from enrollment.[13] (Pellegrino, p. 253).

These kinds of problems are not, of course, new, and it is important repeatedly to hold up the moral shame of the dreadful state of health care for the poor worldwide. And Pellegrino's and others are surely right that the commodification of health care has contributed to this deplorable state.

But my focus will be on another area of heath care that has been dramatically impacted by the growing commodification of medicine, namely biomedical research. Although the medical literature has been increasingly focused on the crisis that the commodification of research has wrought, it has received far too little attention outside of the medical journals. I use the language of "crisis" here somewhat advisedly; I do not want to be accused of exaggeration, but I think there is a crisis in medical research about which we all ought to be concerned. And if "crisis" seems like strong language, it is not nearly as strong as that used by others. Consider, for example, how Jerome Kassirer, the former editor of the *New England Journal of Medicine,* puts this point. In his book, *On the Take, How America's Complicity with Big Business Can Endanger Your Health,* published in 2005, Kassirer documents the way market forces have impacted clinical research in this country.[14] Kassirer doesn't mince words: "whether intentionally or not," he writes, "too many physicians have become marketing whores, mere tools of industry's promotional efforts."

Or consider some of Richard Horton's observations about the corruption of medicine published in the *New York Review of Books* last year. Writing about industry-sponsored medical conferences, he writes: "The venality of those taking part in this corrupt covenant is difficult to square with a profession that is quick to squeal at the mere suggestion of government intrusion into the delivery of health care. Any claim that the science and practice of medicine are disinterested is utterly groundless. Of medical journals, he says: they have "devolved into information-laundering operations for the pharmaceutical industry."[15]

If we turn to examine the implications for genomic research of the growing commodification of science and medicine, we cannot help but be struck by how profoundly biomedical research has changed over the past twenty-five years, particularly in the United States. I cannot provide a full account of those changes today, but it is especially worth noting the shift that has taken place from publicly-funded research to privately-funded work.

The development is dramatic. Whereas in 1980 only 32% of biomedical research was funded by industry, in the year 2000, 62% of such research was industry funded. For example, in the year 2000, the pharmaceutical industry spent approximately $4 billion on grants for clinical trials compared to only $750 million by the National Institutes of Health.[16]

At least in the United States, these changes were propelled by two events, and it is worth saying a word about each. The first is the

passage in 1980 of the Bayh-Dole Act that formalized the process by which researchers who were doing publicly-funded work could seek patent rights on the fruits of their government-sponsored research. Although universities were sometimes able to patent products that grew out of publicly-funded research before the passage of this act, Bayh-Dole made this much easier. Indeed, the whole point of the Act was to provide incentives and a structure that would facilitate moving publicly-funded research from the lab to the marketplace. And there can be little question that Bayh-Dole has been successful in this regard. In the period from 1979 to the present, the number of patents held by universities has increased tenfold.

The second event also dates from 1980, for in June 1980 the U.S. Supreme Court ruled in *Diamond v. Chakrabarty* that the U.S. Patent Office could issue a patent on a bacterium engineered to consumer oil slicks. Although the so-called "product-of-nature" doctrine had historically been understood to prevent the patenting of objects found in nature or living organisms, the court ruled 5-4 that Ananda Chakrabarty's engineered bacterium was not a product of nature but a human invention, which could be patented. As Chief Justice Burger put it, "the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-mode inventions. Like the Bayh-Dole Act, this ruling accelerated the pace of patenting in the biotechnology industry and it opened the door to the patenting of life forms and their constituent parts.

Unfortunately, most of the evidence suggests that this shift from publicly-funded to industry-funded research has been deeply problematic. For example, numerous studies have documented erosion in the tradition of open scientific collaboration as more and more research is conducted with the goal of establishing proprietary patent claims. As these studies document, when research is funded by industry and when patent protection is at stake, there are generally both publication delays and data withholding.[17] Moreover, the financial relationships between industry and individual scientists also appear to have a deleterious effect on the objectivity of the research. As one studied published in the *Journal of the American Medical Association* puts it, "strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions."[18]

Moreover, as universities have come to see basic research as a potential revenue stream, they have not only sought patent protection for the downstream commercial end products of research, but protection for the upstream tools necessary to pursue basic research at all. As Rai and Eisenberg put the point, "Universities have taken the opportunity to file patent applications on basic research discoveries, such as new DNA sequences, protein structures, and disease pathways, that are primarily valuable as inputs into further research..." Rai and Eisenberg note, for example, that 50% of Columbia University's licensed patents are for research tools, namely for "materials, data, and methods that are employed in the research that leads to an end products."[19]

This growing medical entrepreneurialism has thus produced a deeply troubling situation in which the integrity of much research is currently in doubt. So serious are the problems that have grown up around industry-sponsored biomedical research that in 2001 editors from 13 of the world's most distinguished medical journals announced that they would no longer publish research reports about prescription drugs unless the authors assured them that they had full access to all data from the study and were in fact responsible for the work on which they were reporting.[20]

And, given how pervasive the financial relationships are among industry, medical associations, journals, and individual physicians, conflict of interest problems are omnipresent. Consider some of the numbers:

– 43% of investigators receive research-related gifts, including discretionary funds from industry sponsors

– 23-28% of academic researchers in biomedicine receive research funding from industry

– 1/3 of researchers at academic institutions have personal financial ties with industry sponsors[21]

Indeed, the pervasive financial entanglements of researchers and industry led the *New England Journal of Medicine,* in 2002, to abandon its policy of not allowing authors of review articles to have financial ties with drug companies whose drugs were being reviewed, because it could not find enough reviewers without the financial ties.[22]

Now if we want to understand why this growing commodification of medicine should be worrisome in relation to genomic research, we need look no further than the words of John Paul II in his encyclical, *Evangelium Vitae.* When science is understood strictly in utilitarian terms that emphasize economic efficiency, the pope writes:

Man is no longer able to see himself as "mysteriously different" from other earthly creatures; he regards himself merely as one more living being, as an organism which, at most, has reached a very high state of perfection. Enclosed in the narrow horizon of his physical nature, he is somehow reduced to being "a thing", and no longer grasps the transcendent character of his "existence as man".

Like C.S. Lewis before him, Pope John Paul II raised a prophetic voice to call our attention to the future toward which genetic research appears to propel us. Like

Lewis, John Paul was concerned about the "Promethean" attitude toward nature and human life that does not blink at the prospect either of reducing all of the natural world to mere material for our manipulation and use or of genetically engineering a posthuman future. Unlike Lewis, however, John Paul lived, and we live, in a world where the genetic technologies already exist to effect the reduction of the entire world, ourselves included, to the status of sheer matter. In other words, we live in a world where everything is in danger of becoming mere artifact.

I want in closing to give two examples of the Promethean attitude that reduces the world to the status of artifact. In one sense, the examples may seem odd. They are not from the world of science strictly speaking. Indeed, in one sense they are not "serious" examples at all; they are perhaps more playful than profound. Nevertheless, to my mind, they capture the spirit of an age, and they are worth pondering. Both examples are taken from the work of a Brazilian-born, Chicago-based artist named Eduardo Kac. Kac has developed a type of art that he refers to as "transgenic art." According to Kac, transgenic art is "a new art form based on the use of genetic engineering to transfer natural or synthetic genes to an organism, to create unique living beings"[23]

The first example, then, involves an exhibition that Kac mounted in which he specifically addressed the role humans have in the ongoing work of creation as we use genetic technologies to manipulate the world around us. In this work, entitled, "Genesis," Kac created a synthetic gene by translating a sentence from the biblical book of Genesis into Morse Code, and then converting the Morse Code into DNA base pairs according to a conversion principle Kac developed for this work. The sentence in Genesis reads: "Let man have dominion over the fish of the sea, and over the fowl of the air, and over every living thing that moves upon the earth." The Genesis gene was incorporated into bacteria, which could be viewed in a gallery or online.

Visitors to the exhibition could turn on an ultraviolet light in the gallery, causing real, biological mutations in the bacteria, effectively changing the biblical verses that were encoded into the bacterium. According to Kac, the ability to change the biblical verses "is a symbolic gesture: it signifies that we do not accept the meaning of Genesis (or nature) in the form we inherited it, and that new meanings emerge as we seek to change it."[24]

Or consider a second example from Kac's work, an exhibition he undertook a number of years ago to great fanfare. This public art exhibition included Alba, the GFP (green fluorescent protein) Bunny. Alba was an Albino rabbit that glowed green under certain light because it had been genetically altered by the insertion into the rabbit embryo of a gene from a jellyfish that codes for a protein that glows green when exposed to particular wavelengths of light.

Many people were outraged at Kac's creation and many dismissed his work as a publicity stunt, but in fact, part of the point of the Alba project was to generate a public conversation on the cultural and ethical implications of genetic engineering. According to Kac, "the creation of a chimerical animal forces us to examine notions of normalcy, heterogeneity, purity, hybridity, and otherness."[25] Kac's work thus invites us to reflect on the implications of turning non-human animals into artifacts. Specifically, Kac's creation of Alba forces us to ask whether creating unique living beings for our amusement or philosophical edification is morally justifiable. My own answer is that it is not. In fact, I see our willingness to produce transgenic organisms of this sort as symptomatic of a very deep cultural dynamic whereby sentient creatures are reduced to mere objects of manipulation.[26]

I fear that we are, in fact, moving increasingly toward viewing human life in similar, reductionistic terms. The moral challenge we face is how to move forward to realize the great promise of genomic research without turning ourselves and the rest of the natural world into mere artifacts of our own misguided ingenuity. My hope is that conferences like this one will hope show the way.

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Note

[1] B. JENNINGS, "The Liberalism of Life: Bioethics in the Face of Biopower," *Raritan* 22, no. 4 (Spring, 2003): 133-46.

[2] C. S. LEWIS, *The Abolition of Man* (New York: The Macmillan Company, 1947).

[3] G. MEILAENDER, *"Terra es animata:* On Having a Life," *Hastings Center Report,* vol. 23, no. 4 (July-August 1993): 25-32.

[4] Ibid., 29.

[5] Ibid., 31.

[6] The Council's website can be found at: www.bioethics.gov

[7] FRANCIS FUKUYAMA, *Our Posthuman Future,* (New York: Farrar, Straus and Giroux, 2002):70-71.

[8] W. GLANNON, "Identity, Prudential Concern, and Extended Lives, *Bioethics,* vol. 13, no. 3 (2002): 276.

[9] GLANNON, "Identity, Prudential Concern, and Extended Lives, 279-280.

[10] L. KASS, "Ageless Bodies, Happy Souls" *The New Atlantis,* vol. 1 (Spring 2003): 12.

[11] This letter can be found at: *http://212.77.1.245/news_services/bulletin/news/10511.php?index=10511&po_date=11.04.2002&lang=po*

[12] M. CATHLEEN KAVENY, "Commodifying the Polyvalent Good of Health Care," *Journal of Medicine and Philosophy* 24/3 (1999): 207-223.

[13] EDMUND PELLEGRINO, "The Commodification of Medical and Health Care: The Moral Consequences of a Paradigm Shift from a Professional to a Market Ethics," *Journal of Medicine and Philosophy* 24/3 (1999): 253.

[14] JEROME P. KASSIRER, *On the Take: How American's Complicity with Big Business Can Endanger Your Health* (New York: Oxford University Press), 2005.

[15] RICHARD HORTON, "The Dawn of McScience," *The New York Review of Books* 51/4 March 11, 2004, p. 6.

[16] Angel & Relman, 2002: 103.

[17] See Bekelman, Li, and Gross.

[18] JUSTIN E. BEKELMAN, YAN LI, and CARY GROSS, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research," *Journal of the American Medical Association* 289/4 (2003), 463.

[19] ARTI K. RAI and REBECCA S. EISENBERG, "Bayh-Dole Reform and the Progress of Biomedicine," *Law and Contemporary Problems* 66/1.

[20] See MARCIA ANGELL and ARNOLD S. RELMAN, "Patents, Profits and American Medicine: Conflicts of interest in the Testing and Marketing of New Drugs," *Daedalus* (Spring, 2002).

[21] BEKELMAN, LI, and GROSS, p. 456.

[22] See NATHAN NEWMAN, "Big Pharma, Bad Science," *The Nation* July 25, 2002.

[23] Information about Kac's work can be found at: *http://www.ekac.org/gfpbunny.html*

[24] For more on this work, see: *http://www.ekac.org/transgenicindex.html*

[25] For a discussion of Kac's work, see *The Eighth Day: the Transgenic Art of Eduardo Kac.* Sheilah Britton and Dan Collins ed. (Tempe, Az: Arizona State University, 2003). See also the work of the artist Patricia Piccinini at: *http://www.patriciapiccinini.net/*

[26] W. S. Merwin captured the danger of this kind of reductionism in a poem entitled, "Dog": "...Whatever he was to guard/Is gone. Besides, his glazed eyes/Fixed heavily ahead stare beyond you/Noticing nothing; he does not see you. But wrong:/Look again: it is through you/That he looks, and the danger of his eyes/Is that in them you are not there..." in *Green with Beasts* (London: Hart-Davis, 1956).

BONIFACIO HONINGS

4. Towards Liberal Eugenicism: an Ethical Assessment

Science today is by now increasingly learning about the secret of life. It has managed to decipher the gigantic text which in three milliard letters is written into the cells of man. This map of the genome contains the instructions for growing, for developing, for reproducing and for dying. This is knowledge which in a future that is near to hand will not only make almost all illnesses *diagnosable* but will also render certain multifactorial pathologies *treatable*, pathologies such as diabetes, as well as predisposition to vegetative and cardio-circulatory disturbances. Indeed, the techniques of genetic engineering are already able to treat illnesses with a genetic basis by replacing defective genes with normal genes which are introduced through the vectors of the sick organism. I would like to add, to bring out even further the advances in the health-care field, that one of the most recent modalities of therapeutic intervention involves acting on the expression of genes rather that replacing defective genes. From this brief introduction, which is full of hope, on the therapeutic finality of knowledge about the secret of life, I will now move, because this is the task that I have before me, to finalities that have the purpose of 'improvement' (gene enhancement). This paper is organised into two parts. The first, of a historical character, goes from the eugenics movement to eugenicism; the second, of a doctrinal character, deals with an ethical assessment.

From Improvement Eugenics to Liberal Eugenicism

I begin with the fact that the subject of *genetics* has re-proposed in innovative terms the question of *eugenics* because the term 'eugenics' has changed. The eugenics movement goes back to 1870 and until 1950 it revolved around the attempt to 'improve the genetic inheritance of mankind', principally through techniques and strategies of reproductive selection and the promotion of the generation of individuals with a 'good' genetic endowment.[1] This initial stage was connected with the name of Galton and we may define it as 'social eugenics'. This is what we can read in one of his works of 1873: his task was to 'bring forward the slow and stable process of natural selection by striving to eliminate weak constitutions and ignoble and contemptible instincts and to conserve those that are strong, noble and prosocial'. From this stage there was a move towards 'Nazi eugenics' which was described by Hitler in his *Mein Kampf* in the following way (I quote): 'The national state…must place the race at the centre of general life…The state must act as the keeper of a thousand-year future, before which the wishes and the selfishness of individuals are of no account and must bow. The state must to this end use the most modern medical resources…Those who are not healthy and worthy in body and spirit do not have the right to perpetuate their sufferings in the bodies of children…It would be sufficient to impede for six centuries the capacity and the faculty to generate in those who are degenerate in body and who are sick in spirit to free mankind from an immense misfortune and to lead humanity to a state of health that today is almost inconceivable. When this will be carried out in a conscious and methodical way, and the fertility of the healthiest part of the nation is fostered, we will have a race that, at least in principle, will have eliminated the germs of contemporary physical and moral decay'. We ourselves have arrived at the stage that follows the completion of the Human Genome Project and we are drawing near to the liberal eugenicism of the methods of prenatal diagnosis of artificial fertilisation. We may observe a fundamental difference. Whereas in the previous stages 'good generation' was held to be the task of public institutions, now, in liberal societies, genetic decisions are entrusted to the options of individual parents or, as is commonly said in market societies guided by interests, profits and preferences, decisions are left to the 'anarchic wishes of customers and consumers'. To summarise: the relevant characteristic of new liberal eugenicism is the neutrality of the state. Once the entire fan of genetic therapies has been made known to them, the parents of the future will be able to refer to their own values to choose what improvements to give to their children.[2] To have an idea of what liberal eugenicism is I will quote the following: women have a new duty: 'to reject the continuation of the pregnancy of a foetus that is destined to become a human being who is condemned to disabilities and sufferings'. This is a right that may be defined 'to some extent as a duty of a woman towards her child'. If 'we females give birth to an inadequate baby we must then give that child all our help in the eventuality that once grown up he or she wants to commit suicide'. This is because 'the idea that human imperfection should in all cases be accepted belongs to certain religions, such as the Christian religion, which propose suffering as a value'. Instead, liberal humanism can with serenity do without it and aim directly at

technologically up-to-date editions. We should note the point well: one is no longer dealing with a policy of 'social hygiene' or 'racial hygiene'. Nobody today proposes genetics as a strategy for 'ethnic cleansing' of a certain kind, carried out with a Promethean approach of faith by progressives and the champions of free individual choice. [3]

An Ethical Assessment

I will begin with the hope that science and the technique of gene therapy increasingly advance. This is because, at the level of principle, if the finality with which one intervenes upon the genome of a human being, thereby changing it, is strictly therapeutic, that is to say it is directed towards the correction of a defect, or is engaged in to combat a pathogenic factor, such an intervention is morally licit. In fact one is not dealing here with acting on a human subject in order to change his or her genetic identity or with introducing supposed 'improvements' or 'amplifications' in relation to his or her natural qualities, which for that matter are based upon criteria that are inevitably arbitrary and a matter of opinion. Interventions of a strictly therapeutic character in the human genome aim, on the contrary, at restoring the normal genetic configuration of the subject or at combating the damage caused by the genetic anomalies that are present or engendered by other correlated pathologies.[4]

As regards liberal eugenicism, I would like to make clear that this does not explicitly envisage the objective of the elimination of individuals with a 'pathological' genetic inheritance. However, it should be said clearly that a certain selection of individuals on a genetic basis does have the tendency to manifest itself. One need only think here of the systematic spread of pre-implantation and prenatal genetic diagnosis where the possibility of analysing the genome of embryos and foetuses is connected with the possibility of not implanting the first and aborting the second. This connection establishes a situation that spontaneously reduces the births of individuals with genetic defects. Prenatal diagnosis involves an eliminatory selection of carriers both at the embryo and the foetus stage. From an ethical point of view, it is *luce clarius* that the project of liberal eugenicism is morally illicit precisely because it is made up of the objective of selecting the best genetic endowments by eliminating or sterilising the carriers of genetic inheritances that are held to be worse or 'defective'.[5]

However the basic question that should be posed is this: 'can we consider the genetic self-transformation of *the species* as a means to increase *individual* autonomy or will this pathway threaten the normative self-understanding of persons who lead their lives in a way that demonstrates mutual and equal respect?'[6] Can contemporary humanity imprison future humanity; to whom does this power belong? And over whom or over what is this power exercised? [7] The answer is evident: the living of today cannot exercise a power over the men of the future because these last would be the defenceless subjects of decisions taken beforehand by those who plan at the present time. Formulated in the form of a question, the answer is the following: 'what could happen within a person when he or she discovers that 'his' or 'her' body is the result not only of a natural process but also of a technical production that was willed and varied out by other human subjects? The young person who has been genetically manipulated would discover that his or her own body is something that has been produced technically. The perspective of the life experienced by the subject enters into collision with the objectifying perspective or his or her producers and experimenters.[8] To summarise, and here I conclude, the basic reason for the illicit character of eugenicisim, whether liberal or otherwise, when the nature of the natal is modified, is that with this is also modified the profound nature of human action. The freedom of the person would no longer lie in the possibility of him or her being the 'author or authoress' of his or her own actions: he or she would only be a 'repeater' of technically manipulated processes. But there is yet another concern, namely that connected with the future of equality amongst men. There is the risk of introducing into humanity an interpersonal relationship that is 'unprecedented'. Children, with respect to their birth, depend upon parents and thus their relationship cannot be inverted. This dependency regards pure existence and not their nature. St. Thomas would say that one is dealing here with a dependence '*in fieri*' but not 'in being'. This is not an equal relationship. The parents are not the '*causa essendi*' of their children. Thus any social, racist or liberal eugenicism not only removes the freedom and equality that is specific to human nature but also removes the moral life itself.

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Note

[1] Cf. MARINA VALENSISE, 'Bioetica, ma senza dogmi', *Il Foglio*, 13 March 2003.

[2] N. AGAR, 'Liberal Eugenics', in H. Kuhse-P. Singer (ed.), *Bioethics* (Blackwell, London, 2000), p. 171. Cf. BUCHANAN, BROCK, DANIELS, WIKLER, *From Chance to Choice: Genetics and Justice* (Cambridge University Press, Cambridge, 2000).

[3] Cf. EUGENIA ROCCELLA, 'Eugenetica liberale. Se per la donna il diritto di rifiutare il feto difettoso diventa un dovere', *Il Foglio*, July 2005.

[4] Cf. M. CUYÁS, 'Problematica etica della manipolazione genetica', in *Rassegna di Teologia*, 1985, 5, 471-497.

[5] Cf. 'Etica ed eugenetica', *http.://www. univ. trieste. it/-etica / 2004 2/ mordacci. htm*

[6] J. HABERMAS, *Il futuro della natura umana. I rischi di una genetica liberale* (Einaudi, Turin, 2002), p. 31.

[7] Cf. H. JONAS, *Tecnica, medicina ed etica: prassi del principio responsabilità,* Italian editino edited by Paolo Becchi (Einaudi, Turin, 1997).

[8] Cf. HABERMAS, op. cit. p. 52.

KARL LEHMANN

5. The Prevention of Genetic Illnesses from the Point of View of Pastoral Care

1. Introduction

In 2004 public opinion was surprised by the news, six years after the establishment of the human genome project and five years earlier than had been predicted, that the genetic inheritance of humans had been almost completely decoded (see the edition of the journal *Nature* of 21 November 2004). In all, the human genome has 2.85 million of pairs of bases and information for twenty thousand to twenty-five thousand genes. Whereas ten years ago it was believed that a human being had a hundred thousand genes, by now reference is made to a fifth or a quarter of that figure. On the basis of the almost complete sequence that is now available, more precise studies can be carried out on genes and it is possible to identify with greater certainty the alterations that cause illnesses. One should not underestimate the role of these data in clinical research, in the research carried out by the pharmaceutical industry, and even directly in our lives and our health. From genetic engineering valid information can be obtained that can prevent illnesses and reduce pain.

The positive outcome of the human genome project has been celebrated as the 'completion and crowning of the hundred-year old history of genetics' (Zoglauer, 13). However the hopes involved are counterposed by a very large number of risks and ethical questions and problems that have not yet been completely clarified, issues such as obligations in relation to the feasibility and possibility of carrying out genetic research, the treatment of sensitive genetic data, the reduction of the human being to his or her genes, the stigmatisation of the sick and of the disabled, as well as the danger of eugenic tendencies (Habermas 2001a, 34 ss, 105 ss).

In order to engage in an adequate assessment of the risks and opportunities of the human genome project, one should first look with a critical eye at the subject of this research, namely the human gene. The theory that the essence of a human being can be traced back to his or her genes, that the human being is nothing else but the sum of his or her genes, and that therefore he or she can be determined through the control of his or her genetic structure – this idea suggests that forms of life and their expression that deviate from the norm because of defects in the genetic structure are to be condemned. Genetic engineering, it is argued, thus has the task of favouring positive characteristics and eliminating disadvantageous elements. Just as we are already able to see individual genes as factors that generate specific hereditary diseases such as cystic fibrosis, muscular dystrophy or degenerative chorea, and to identify genes that cause obesity and breast cancer, so also it is hoped that soon it will be also possible to explain other maladies in genetic terms – psychoses, schizophrenia, a tendency to alcoholism, and so forth.

This, however, assumes that a gene is always responsible for a specific process – gene X is said to be responsible for brown hair, gene Y is said to be responsible for intelligence, and gene Z is said to be responsible for obesity. Research, however, has demonstrated that genes 'are not responsible for something' but, instead, provoke something. A gene can codify different proteins and thus be responsible for various characteristics. There are, instead, characteristics that are the result of the interaction of a number of genes. In this way about twenty thousand human genes produce more than a million different proteins (cf. Zoglauer, 14). Similarly, there are illnesses that cannot be associated directly and clearly with a specific gene; indeed, the majority of hereditary diseases are not monogenic in origin but find their causes in more than one gene.

To this should be added that not only specific genes or interactions between various genes decide if and to what extent an illness emerges or a certain feature or form of behaviour of that illness. Environmental factors play a significant role here: the social environment in which a human being grows up has a part to play, as do his or her lifestyle, diet, culture, education and other factors. From this fact one already understands that the theory according to which man is nothing more than the sum of his genes is not a valid one. 'Man is not the outcome of his genes or his environment but the result of the interaction of both, an interaction which begins in the womb and is influenced, for example, by the hormones of the mother' (Zoglauer, 15). The theory according to which the gene 'is the real master of the human being' (R. Dawkins) and that the human being in essence and behaviour is nothing else but a puppet determined by selfish genes is too limited and does not do justice to the complex results of the research that has been carried out in this field.

Biologists are increasingly of the view that a human being can be influenced in his or her behaviour but is not completely determined by hereditary factors. To this is added the fact that in the prenatal

stage of a human being's existence chance factors have a determining influence on the replication of genes, the division of cells, the growth of cells, and the development of the brain. The hereditary factor must not, therefore, be underestimated. If a human being during his or her life has to address illness and disability, how he or she reacts to developments deemed to be 'pathological' and 'abnormal' in character does not depend exclusively on hereditary factors. Defects in the genes do not necessarily lead to the appearance of an illness but are, possibly, supplementary risk factors. 'The phenotype of a human being is not a causal consequence of his or her genotype. This is because the genotype is not the exact copy of the phenotype' (Zoglauer, 20). One should reflect on these relationships in order to arrive at an assessment from the point of view of pastoral care of the role that genetic engineering plays in avoiding illnesses. It is precisely from this situation that there derive the challenges and the duties of pastoral care that, indeed, correspond to its original task.

2. Genetic Diagnosis and Predictive Medicine

The prospect of also being able to identify, through the help of the human genome project, predispositions to illness offers the possibility of preventing in a planned way these illnesses through the pursuit of a suitable lifestyle as well. However, a predisposition does not necessarily lead to its matching illness. And the fact that each human being possesses a certain number of defective genes means that society is asking itself whether in the future one should really mean by the word 'illness' every deviation from the genetic norm. There thus exists the danger that concepts such as health, illness and disability, which are marked by new characteristics, may be partially redefined in an arbitrary way and the concept of 'genetic disease' may be broadened further. Concepts such as health, illness and disability could be interpreted as biological-genetic standards but also as deviations. The human being could become a mere object that should and could be evaluated.

The analysis of the human genome and the drawing up of a gene map are the point of departure for so-called predictive medicine. The recognition of the fact that specific illnesses are programmed in the genes, and that more illnesses than were previously thought derive from interactions between genes and the environment, has contributed to the development of this form of medicine within the sphere of genetic engineering. Predictive medicine has the aim of predicting the biography of illness of a human being and of identifying that person's genetic predisposition to specific illnesses, so as to then avoid their appearance or at least to influence their development in a positive way. Whereas traditional diagnosis can observe a pathological alteration only after its appearance, a genetic diagnosis is characterised by the fact of being able to predict an illness or a predisposition to an affliction years and even decades before its actual outbreak. Early diagnosis carried out by predictive medicine offers possibilities of treatment and thus means that treatment will perhaps not be necessary after the outbreak of the disease.

Predictive medicine also seeks to avoid the transmission of genetic illnesses from parents to their children. The risk of an affliction thus becomes reduced. For example, one could prevent cardio-circulatory diseases through a correct diet and sport or skin cancer by avoiding exposure to intense sun. At least there would be the possibility of mitigating the development of illnesses with a genetic origin or correlated illnesses. However, one should not overestimate the possibility and the capacity to modify behaviour, as, indeed, has been demonstrated by the experience of practical medicine.

It is estimated that the data and the information obtained by the human genome project will enormously increase the possibilities of diagnosing genetic characteristics, and above all those genetic characteristics that are responsible for the outbreak of illnesses. At the present time, in Germany, there exist genetic tests for more that a hundred diseases. Amongst these we find the genetic analysis for retinoblastoma in order to identify a rare tumour of the eye that is found only in children. The predisposition to this malady can be tested immediately after the birth of the child. If there is a predisposition, the eye of the child is examined at regular levels in order to identify early on the first stages of the tumour and then eliminate them.

Family polyposis is a hereditary form of cancer of the intestine. Employing a genetic test, doctors can identify the mutated APC gene and rapidly adopt life-saving measures. Another example in the field of predictive genetic diagnosis is being able to predict what the level of probability is that a woman will fall ill with breast cancer of a hereditary kind. In 1994, both the anti-oncogenes BRCA1 and BRCA2 were described as genes involved in this kind of predisposition. The difficulties of the genetic test for breast cancer arise from the fact that one cannot not yet make a certain differentiation between the innocuous variants in the basic sequence of genes that produce breast cancer and pathological mutations. Normally these genes impede the formation of breast cancer. But in women with a defective breast cancer gene the risk of falling ill from this tumour at some time increases by 85%. For this reason, some of these women have both their breasts amputated for preventive reasons because they are afraid of getting breast cancer. Here genetic analysis serves only to prevent illnesses: 'there have

been cases where after such an operation (the reference here is to the preventive removal of the breast), in the remaining residues of the epithelium of the covering (a kind of skin of this organ) or in the peritoneum 'breast cancer' emerged, or at least a cancer provoked by the mutated gene BRCA-1' (see Zoglauer, 27).

As regards the risks of predictive medicine, it should be observed that it is to be feared that our society will further reduce the acceptance of illness and disability because of predictive medicine.

Illness and disability, or, to express the point in more severe terms, the sick and the disabled, can be avoided. Already today, abortions are engaged in because of prenatal tests. From the outset a sick or disabled child is not accepted. From an ethical point of view, this is 'a very worrying development that cannot be accepted'. The impact on the disabled of this evaluation by our contemporaries cannot be predicted. With the coherent application of predictive medicine a further opportunity could be created to circumscribe the complex outbreak of the illness to a few factors inherent in the individual. The cause of the illness could be shifted onto individuals and the illness could thus become a personal and private destiny. Other factors, such as an unhealthy or morbogenic environment, could be neglected. The sick person would himself be responsible for his or her illness. One could also create the danger that human beings would be classified and discriminated against from various points of view. One may also fear that human beings will be considered in a biologistic way and reduced solely to their genetic inheritance. In this way, a contradiction with the Christian image of a human being in his or her totality would thus be created.

Another field in which one can prevent illnesses by employing the methods of genetic engineering is that of genetic analyses applied to employees. These allow the observation of genetic dangers at an occupational level and can contribute to an improvement in the defence of individual workers, to preventive medicine at the level of work, and the prevention of occupational illnesses. On the other hand, there already exists the possibility of using such analyses against workers if their genetic make-up is employed as an important criterion in their selection for job. In this way, the possibility of obtaining a job is significantly reduced. One may also perceive the danger that the information gathered on an employee could be employed in a way that goes beyond ascertaining whether that person is suitable for employment.

From an ethical point of view, one should also observe that a genetic analysis can only be carried out if there is a prior authorisation to do so on the part of the employee. In addition, only genetic predispositions that lead to fears about a possible grave damage to the health of an employee or to the health of third parties can be tested for. A genetic analysis should be authorised only when other diagnostic methods do not allow the obtaining of comparable kinds of information. Furthermore, the right to personality of the employee prohibits the acquisition of a complete profile of his or her genetic characteristics. Every human being has the right to self-determination in relation to information about him or her and cannot be stigmatised or discriminated against because of an ill-judged revelation of his or her genetic inheritance. Nobody should be disadvantaged because of their genetic characteristics.

It should be clear that the analysis and the examination of the sequence of the human genome, connected with predictive medicine, make available a very significant form of power. And like every other form of power it cannot only help – it can also destroy. Biological research and its discoveries already widely influence the idea that we have of what a human being is. In addition, for the survival of mankind further research is indispensable, even though this survival will, at least potentially, be threatened by such research.

3. Comments on the 'Right to Know'

Given that in the field of genetic analysis the distance between diagnosis and therapy is constantly increasing, medical doctors and patients find themselves faced with the grave problem of having to adjudge what is most in conformity with the dignity of the human being – whether to become aware of an imminent incurable illness or whether not to become aware of it. There will be a multiplicity of diseases and predispositions that can be diagnosed without an effective therapy for them being available.

The proposal has even been made, in line with the 'criterion of preventive advantage', of not diagnosing diseases with a genetic origin that cannot be treated.

The right to know is opposed here by the mercy of being unaware. In relation to illnesses that can be diagnosed but not cured the advantage of knowing, obtained thanks to genetic analysis, allows a person to organise his or her lifestyle in a suitable way, to plan that lifestyle and to change his or her way of living. However, on the other hand, there exists the disadvantage of knowing and of losing vital energy, hope in the future, and the happiness of the joy of living without fear of illness.

In addition, knowledge about the genetic inheritance of individuals and of groups, if it ends up in the wrong hands, can cause injury, destroy prospects, and ruin life projects. The right to know and the right not to know are two sides of the same coin. Both the former and the latter derive from the idea, which is inherent in the history and the civilisation of the West, that a human being is a person who has the right to self-determination. This concept also contains, as an essential aspect of the idea of human dignity, a prohibition on exploitation, the obligation to engage in the approach based on ends (Kant), and the person's right to his or her private sphere and freedom. All the approaches that lead to the avoidance of genetic illnesses must take these requirements into account. Unawareness can be a 'preliminary condition of freedom' (H. Jonas) because the predestination of future pain, a presumed awareness of one's own future itself…can obstruct the free and spontaneous development of the personality' (Zoglauer, 37). The maximum possible knowledge of a genetic disposition to illness is not in itself a guarantee of health and a happy life, in the same way as the natural and fundamental elements of human nature should not be eliminated. 'With genetic diagnosis there is a somewhat greater raising of the 'natural veil of unawareness' and with gene therapy a human being can modify the destiny that has been assigned to him or her. How this is modified does not matter – new genes provide merely a new destiny to which one must adjust'. These reflections, made in essential terms by H. Jonas when discussing 'the right not to know', are worthy of note if one asks, in relation to today's rationality, why it is that so many people reach this approach and continue with it. This, however, involves a foregoing of something, a foregoing which is in absolute harmony with the creation itself in a Biblical sense.

4. Genetic Consultancy: Possibilities and Consequences

Genetic consultancy and prenatal diagnosis have the task of assessing the risks of the outbreak of certain hereditary illnesses and to reveal or exclude lesions early on. All of this is closely bound up with research on the human genome.

Genetic consultancy

Genetic consultancy, even before procreation, can provide information on whether and with what probability certain hereditary diseases will be transmitted to the child. In cases where one can already exclude through genetic consultation that a future child will suffer from a specific hereditary illness the decision whether to have a child or not is facilitated. If, on the other hand, during the tests a greater risk is determined, those who have asked for advice can take a responsible decision in favour or against procreation with an awareness of the probability of a disease that is present. Genetic consultancy can, therefore, avoid conflict over a future pregnancy. It can also help to ensure that the partners prepare themselves in time for the corresponding risk of a disabled child and can take advantages of all the possibilities of help. Free will is the inescapable premise of the morality of genetic consultancy. Thus any set of rules that make provisions of the state, insurance against illness and welfare provisions depend upon whether a genetic consultation has taken place must be excluded. In public debate, at times, one hears it stated that society has a legitimate interest in avoiding the procreation of gravely disabled children. On the one hand, it is said, society should support the costs of assistance, but on the other, it is asserted, this would worsen the genetic inheritance of the population. One must strenuously oppose such eugenic statements.

Prenatal diagnosis

Differently from genetic consultancy, prenatal diagnosis (PD) – the major field of application of genetic testing – can determine in a pregnancy that is underway whether the foetus is affected by the feared disease or disability. Given that an increasing number of new born children are born with one or more serious lesions of a genetic kind or lesions which emerged during pregnancy – the indications vary from between one to three per cent – one has to acknowledge the need, as regards responsible parenthood, for complete information and consultancy in helping decision-making. This is especially the case if grave family genetic afflictions or external factors generate fears that there is a greater genetic risk involved.

In prenatal diagnosis using amniocentesis and in chorial biopsy foetus cells are removed from the womb and then examined employing cytogenetic methods and a direct analysis of the DNA to look for genetic deviations. Where the existence of the feared genetic deviations is confirmed, therapeutic measures can be applied as quickly as possible and pregnant mothers can be offered those forms of help that will allow them to adapt to a possible illness in their child. At the present time, there are therapeutic options for many hereditary diseases only in very rare exceptional cases. A success at the level of therapy was obtained in the United States of America in 1998. It was possible, by engaging in an operation on the foetus in its mother's womb, to correct at least in part the genetic malformation of spina-bifida of the unborn child.

From an ethical point of view, prenatal diagnosis involves a conflict between the life and the welfare of the unborn child, on the one

hand, and the needs, the wishes and perhaps also the rights of its parents, on the other, because here there is a divergence between law and ethics. The theological and ethical judgement on prenatal diagnosis is unequivocal. PD is in itself neutral from an ethical point of view. An ethical qualification applies when there is a practical application. If it fosters methods for the safeguarding of the health and the treatment of the unborn child and if it useful in allaying the concerns of worried parents, then prenatal diagnosis is morally useful. It can also facilitate the decision to have a child even in cases of pregnancy at risk – in 97% of cases the parents after one month can be freed of the unjustified fear that they will have a disabled child. One should not forget this liberating and positive form of help and assistance.

In other cases the parents can habituate themselves over time to the idea of a disabled child. Prenatal diagnosis can, in addition, avoid pregnancies being interrupted simply because it is suspected that the unborn child will have probable lesions. And, lastly, prenatal diagnosis is of use in the struggle of medicine against foetal illnesses because very early on – during pregnancy, at the moment of childbirth or immediately after the birth of the child – it allows optimal preventive or therapeutic treatment. If, instead, prenatal diagnosis is carried out with a view to engaging in an abortion where the unborn child has an illness or a handicap, it cannot be justified at an ethical level. John Paul II observes in his encyclical *Evangelium vitae* of 1995 (n. 63): 'But since the possibilities of prenatal therapy are today still limited, it not infrequently happens that these techniques are used with a eugenic intention which accepts selective abortion in order to prevent the birth of children affected by various types of anomalies. Such an attitude is shameful and utterly reprehensible, since it presumes to measure the value of a human life only within the parameters of 'normality' and physical well-being, thus opening the way to legitimising infanticide and euthanasia as well'.

As regards the weighty set of questions and issues that accompany prenatal diagnosis, in the contemporary debates one may detect a new way of thinking, which began first and foremost with the female movement, with associations of disabled people and with the Churches. Strong tendencies are now emerging to ensure a reconsideration of the way in which prenatal diagnosis is disciplined and regulated.

Pre-implantation genetic diagnosis (PID)

Pre-implantation diagnosis is a further possibility at the level of application in the field of genetic analysis and relates to the prenatal stage. Indeed, with the technique of pre-implantation diagnosis genetic diagnosis has taken a further step forward. Thanks to this method of analysis couples with hereditary diseases are helped to have a child. The embryo that is conceived *in vitro* is examined at the eight-cell stage before it is placed in the womb in order to ascertain if it is genetically healthy or whether it has inherited a pathological trait from its parents, that is to say the feared genetic defect. In case of a positive result of the test the embryo is not transferred into the womb but destroyed. Selection is an obvious feature of this method and thus we can already see the move from a negative selection, which prevents the development of human beings with a genetic defect, to a positive selection based upon eugenics, with the aim of only allowing those embryos that have certain wished for characteristics to survive. These diseases, characteristics and predispositions have to be placed in a catalogue of indications for PID which seems to depend more upon discretionary powers and various interests rather than upon rigid and objectively sharable arguments which are also sustainable from an ethical point of view and in sociopolitical terms. 'There are indications of a desperate attempt to avoid the breaching of a moral dyke' (Zoglauer, 44). Even if attached to a rigid catalogue of indications, pre-implantation genetic diagnosis is declassified because of its immanent methodology of selection and becomes absolutely unsustainable from an ethical point of view. It also fails as a measure for the avoidance of genetic illnesses.

New therapeutic possibilities: gene therapy

With an increase in the possibility of identifying genetic defects, the probability of repairing them also augments. Gene therapy has the aim of treating genetic diseases or maladies correlated with them or to ensure that such illnesses do not even appear. This takes place either through the elimination of symptoms or through the removal of the cause of an illness. At the present time, gene therapy is only suited to the treatment of hereditary illnesses caused by a single gene and dependent upon the modified structure of that gene. When the illness is caused by more than one defective gene or by the interaction of defective genes or by environmental factors then reference is made to multifactorial causes. At the present time and also in the near future the treatment of illnesses caused by a number of factors through the employment of gene therapy is excluded.

Gene therapy as the completion of the forms of therapy that already exist has a fundamentally ethical legitimation thanks to the dignity of prevention and repair which is directed towards the achievement of human health and thanks as well to the hoped for reduction in pain. Both these therapeutic approaches are, however, relevant to a deeper ethical assessment.

In the case of somatic gene therapy, which is directed at cells of the body that no longer function in a regular way, there are not, in general terms, new ethical problems as compared to traditional forms of therapy. Somatic gene therapy must be assessed in the same way as all other new therapeutic methods are assessed. This means that the method must be safe, it must be proportionate, and the patient must give his or her informed consent.

Gene therapy in relation to the germinal line is, instead, an intervention upon the genetic informa-

tion of these cells from which the germinal cells (the germinal line) come. It can also form totipotent cells on the same germinal cells, on the fertilised cells, and upon the embryo cells. Differently to gene therapy, therapy applied to the germinal line provokes not only a change in the human beings involved themselves to whom it is applied but also determines the genetic characteristics of the descendants of these individuals. Germinal line therapy is not a practical possibility at the present time nor will it be so in the immediate future.

Pragmatic and categorical arguments are at the base of it being ethically unsustainable. The practical arguments refer first and foremost to the risks that are involved: one would not be able to exclude that these interventions will cause irreparable damage and provoke changes to the personality. There is also the danger that these modifications would be used in an illicit way in the generation of human beings. In addition, in order to develop this therapy experiments with human embryos are required which would have to be rejected in the interest of the primacy of the protection of life over the protection of health. The categorical arguments that are employed against germinal therapy lay down that this method is an offence against the dignity of the human being because it modifies the genetic basis of the individuality of a person and thus his or her personal integrity.

Each human being enters society as a generated and born person and not as a person who has been made and selected. That human being has his or her rights and does not have to render thanks to anyone. If a fertilised cell is subjected to an intervention involving genetic engineering, even for a medical purpose, an existing person is not treated. What happens here is that his or her identity is manipulated. In violating the generations to come, the knowledge of genetic engineering of our time could lead to an increasing power over future generations. This would mean, from the point of view of those generations, that knowledge could lead to the dominion of the dead over the living, and this is something that would be absolutely irreversible.

New pharmaceuticals

There are possibilities of applying genetic engineering in the field of the development of pharmacology which have as their goal that of preventing or curing illness. From the point of view of the ethical protection of health, it would appear irresponsible to forego the new opportunities at the level of the production of pharmaceuticals that have been opened up by genetic engineering or to forego improved opportunities at the level of therapy. The development of new active substances could be very relevant in the fight against tumours and in the treatment of people suffering from Alzheimer's disease.

The so-called protein pharmaceuticals form a part of this category of pharmaceuticals of a new kind which have been produced by genetic engineering. They provide sick people with the proteins that they are not able to produce in sufficient numbers themselves. Another gene pharmaceutical product which is now known about on the pharmaceutical market is human insulin for the treatment of diabetes.

5. Pastoral Help – Repercussions above all in Relationships with the Disabled

With the analysis of the human genome and predictive medicine, life has become, after a certain fashion, more predictable. However, the more medicine is able to provide something similar to 'guarantees' about a healthy child, for example through the employment of prenatal diagnosis and pre-implantation diagnosis, the more the rejection of damaged or disabled life grows greater. One may certainly expect that people's readiness to accept handicapped human beings from birth and to see them as a task for the whole of a lifetime will diminish. Perhaps one day society will not even accept disabled children. It will be known that they could have remained unborn and in the final analysis all legal possibilities available could be used to eliminate them before their birth. There may even be an upholding of the right to have a healthy child.

The burden that a disabled child represents for a family is serious and onerous. But in such a family as well joy and happiness are not excluded, event though the life of that family is always marked by this disability. How can one reconcile the principle that life is a blessing and a gift if the conditions of the life of a disabled child at times oppress a family in an unspeakable way?

In the Christian message it is God, who blesses and gives life, who provides an answer to this question. Jesus Christ experienced pain and suffering in his life to the point of being 'forsaken' by God on the cross. In this world we constantly see, at times in a painful way, that even the creation is broken, but God shares in this and thus we can hope. Contrary to our natural desires, we can accept and appreciate the weak, the incomplete and the suffering. There thus begins a pathway of humanisation, of profound respect for life, that pathway which was pointed out to us as the pathway of salvation. Wherever there is a person who because of faith or human honesty is on the side of this destiny and does not withdraw from it by destroying life, that person achieves possibilities for maturation at a human level which would be unreachable without suffering. Every pastor of souls knows of concrete examples where this is very tangible. All of us owe to these parents and these families who have begun

to go down, and continue to go down, this path, gratitude, consideration and active help. This is an important task that is often neglected by spiritual assistance in these situations.

Where medicine and genetic engineering meet their own limits because they, too, cannot guarantee a life without suffering, illness and disabilities, it is the primary task of the Church and pastoral care not to leave these afflicted people alone on their difficult pathways, to help them to accept the destiny of illness and disability, and to encourage them, notwithstanding all the adversities, not to lose their faith in the meaning and the dignity of every human life. It cannot be the task of pastoral care to expect salvation only from modern bioscience. The Church in her preaching and in her service to the sick must show that a human being can achieve final and definitive healing only in faith in God. In her spiritual assistance the Church must not fail to be near above all to those whom medicine cannot help.

Christians believe that a human being has his or her origin in the mystery whose existence men intuit, through their research and their questions, behind their lives, what Christians call Jesus Christ, God. For Christians, human life, in whatever form it takes, is never absurd and useless. A human being is not the outcome of chance. A human being did not create himself or herself and a human being does not exist in a state of absolute autonomy. For this reason, he or she cannot guarantee the meaning and the value of his or her life. The belief of Christians that man is created by God contains the message that every human being is willed, accepted and loved by God, and is called to find the happiness of his or her life in union with God. For Christians, the inalienable dignity of the human being is based on the fact that beyond all his or her abilities, capacities and incapacities, he or she is loved unconditionally by God and is accepted by God in definitive fashion. Christians believe that God guarantees the value and the meaning of every human life. A human being can only be told by God what are the meaning and the value of life and accept them with faith. Christians believe that God does not abandon men but remains faithful to them. God broke the hellish circle of hopelessness, uselessness and guilt through the birth, life, death and resurrection of Jesus Christ. In making Himself man, God placed himself definitively on the side of every man and confirmed human dignity in an insuperable way. In Jesus Christ, God Himself shared in the destiny of human beings in joy and hope, in failure and suffering, until the hopeless of death. God, in Jesus Christ, is at the side of the man who is not recognised, who suffers, who is nailed to the destiny of his disability, which apparently can no longer give anything, who is defeated in his life, and who dies. When God raised Jesus Christ from death to the fullness of life, the believer was given the certainty and meaning that God is faithful to him, that He does not abandon him even in suffering and death. In his belief in God, man finds the future and the meaning of his own life (Lehmann 2005).

If the Church acts against abortion that is carried out because the unborn child involved has an illness or a disability, she must also commit herself in a human way to helping the parents of disabled children and act in a solidarity-inspired way towards them. Parents must also feel esteem for the love that they give to their disabled child in the environment that surrounds them. If we allow this not to take place we sin against them and against their disabled child, and also against the divine gift of life, which the majority of us received without any such disability. We should all create an atmosphere of trust and of acceptance of a child who has a handicap and of his or her parents. Each one of us should do everything that is possible to ensure that our parishes become communities of joy in living and of trust in life. The contact groups and the self-help groups can contribute to ensuring that disabled parents and their parents are not neglected as they experience their difficulties.

This means helping them with a form of assistance that is directed towards alleviating the burden of the multiple tasks which, when taken together, appear to constitute a situation that it is difficult to bear and a situation that is almost hopeless. This can also be done by providing a large number of small forms of help in daily life which will help the parents to overcome many difficult situations. The Church should also promote, to the extent that this is possible, through preaching and the service that she provides, a strengthening of comprehension, responsibility and sol-

idarity, and she should attend to urgent needs in a way that is not bureaucratic in method. Spiritual assistants should never tire in looking for a way by which to draw near to the disabled and their families.

For a Christian community no form of suffering must remain extraneous to it if that community takes seriously the image given by St. Paul of a Christian community as the 'Body of Christ' (Rom 12; Cor 12) . Each human being is a part of this body. The pain of one part of it is the pain of all of it. Detachment from the suffering of another person must therefore be understood as detachment from the body of Christ. Compassion for, and solidarity with, the suffering, are essential elements of the Christian existence. From this concept of the community as the body of Christ comes not only the deaconry for the sick and the disabled but also the deaconry of the sick and the disabled for society. 'Paul does not believe that this Body of Christ is bursting with health. There are weak parts and there are delicate parts. And God gives to the delicate member the greatest consideration and the greatest splendour (1 Cor 12:24) because He needs the weak and delicate members for His Kingdom. Why? Because the community of the Body of Christ is not only the community of the Christ who rose again but also that of the crucified Christ…The Body of Christ is also the body of the Son of weak, helpless and crucified man. And the strength of the risen Christ always lies in union with the sufferings of the Crucified One' (J. Moltmann).

The sick and the disabled and their families still do not receive sufficient consideration in public. Here the Churches, even more than they do now, must raise their voices and speak for the dumb (Wis 31:8), speak as an advocate for those whom illness and suffering have rendered mute. Illness and its needs have to be publicised because help, on its own, cannot pass through closed doors. The churches and above all the local communities must become aware of all those encumbrances that have not as yet been removed by society and social assistance. Through the communities one can offer personal help in a direct way to sick people and their families. In this way the encounter with one's neighbour will be strengthened and sick people and their families will experience within the community the promise and the meaning of life.

6. Conclusion

The analysis of the human genome that has been carried out presents less ethical and pastoral problems than the possibilities to which it gives rise. These possibilities must be subjected to control in order to see whether they act to protect and promote human life, improve its possibilities, and defend important ethical values, or whether, in contrary fashion, they are in opposition to such things. It may be proposed as a first rule that one should not diagnose more than one is able to do from the point of view of prognosis and therapy. The great advantage of genetic analysis is to be found in the fact that it allows individuals to act in a responsible way in relation to their own health or that of their descendants. This does not mean, however, that people can be obliged to know more about themselves than they want to know (the right not to know). The use of genetic analysis for selection is ethically unacceptable and ethically problematic. Prenatal diagnosis often leads to abortion; the screening of workers often results in a preference for physically robust employees; and in health insurance genetic analysis can lead to worrying disparities from a socio-political point of view. Given that the data obtained through the employment of genetic analysis bear upon the core of the private sphere, no person can be obliged to reveal them (the protection of data) except where it is feared that grave damage will be caused to third parties. In addition to the risks for the individual sphere, we also find opportunities presented to us by the development of new diagnostic methods, new pharmaceuticals, and new therapies. For this reason, genetic analysis is not only advisable but also corresponds to the nature and the creative task of a human being who, in a responsible way, takes in his or her hands his or her genetic destiny and does not merely leave it in the hands of nature or biological evolution. The risks involved must be limited by responsible actions, directives and possible laws.

On the basis of the possibilities that have been indicated it seems neither possible nor reasonable, nor indeed ethical, to accept or demonise modern genetic engineering, the human genome project, and the predictive medicine that is so bound up with this project. A rapid identification of illnesses that are in part mysterious, and the possible therapeutic opportunities involved, can avoid a great deal of suffering. However one should ask, taking into consideration the general effect of the options provided by genetic engineering and of each individual intervention, about the extent to which life is protected, defended and saved and whether one is helping a human being to have a life that is worthy of man. In this context one should open a debate about illness and disability because only in this way can one avoid the stigmatisation of, and discrimination against, the sick, the disabled, and people who possess unfavourable hereditary factors.

Even with so many genetic data on the structure of human beings we are not able to find the meaning of human existence. Human beings find the meaning of their lives not in their genes but on how they manage with their own 'nature' their social, personal and religious relationships. The meaning of life is more than mere functioning. This is not a fact but a matter of faith. He who possesses faith can move mountains. Concepts such as 'gene' or even 'humanity' are not subjects to which the individual should be sacrificed. They are, instead, abstract instruments of rational information. Biological knowledge can certainly allow more aware human actions but it cannot replace the personal perspectives of life.

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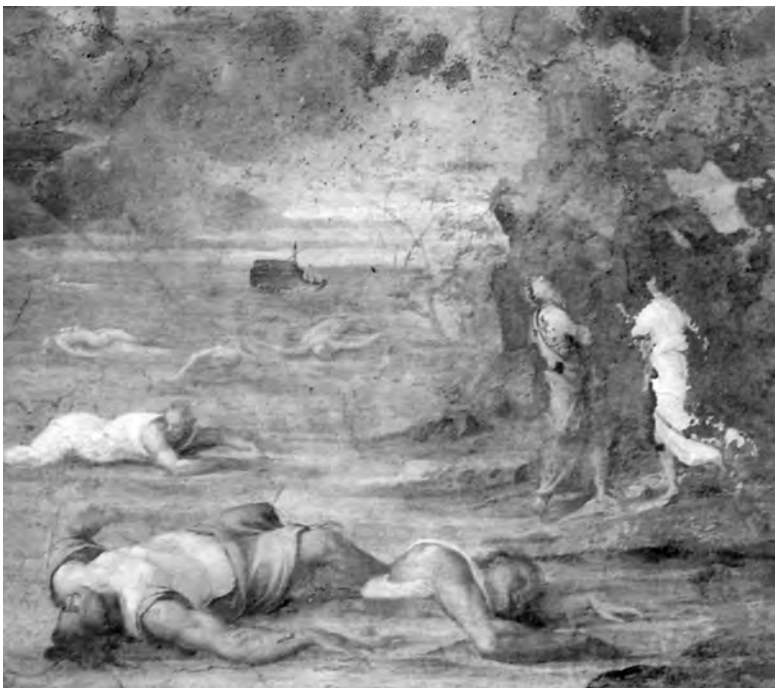

6. Inter-religious Dialogue on the Application of Human Genetics Knowledge

ABRAMO ALBERTO PIATTELLI

6.1 The Jewish Perspective

The unprecedented advances achieved by genetic and biomedical research in recent decades has not only produced new perspectives as regards the nature of life and its most intricate processes: we have also witnessed revolutionary changes in the practice of medicine and in applied research. Given that the life of man is at the centre of so much attention, it is evident that the Jewish religion cannot remain extraneous to these innovations and must be attentive to addressing the specific implications involved and to expressing its opinion on the serious and numerous problems that arise every day.

Knowledge and its pursuit constitute legitimate activities for human beings and do not amount to interferences in the divine prerogatives. But the debate on genetics is becoming increasingly vast, and often increasingly dramatic, faced, as it is, with the prospects offered by the advances in genetic technologies.

In my opinion it is difficult at the present moment to engage in a univocal and absolute analysis from a Jewish point of view of the questions and issues that are raised by genetics. Indeed, it is necessary to examine individually the various aspects that this science deals with and to manage to formulate a judgement that cannot be generalised. It is difficult to follow this pathway in the short amount of time that is available to me. Each case should be studied and discussed individually in order to examine its implications and its implicit shades of significance.

Thanks to research in the genetic field, it is possible to diagnose and understand in an ever better way, during the prenatal stage as well, those hereditary diseases that our society, unfortunately, has to face up to every day.

But there could be illicit speculations in the field of this discipline that could lead to real and authentic aberrations. What should we say, in fact, about what is continually called 'genetic engineering' or the techniques involving the cloning of human beings and the enormous moral and social implications that could spring from them?

An examination of so many aspects of biomedicine, from organs transplants to *in vitro* insemination, from the freezing of bodies to euthanasia, and so on, in addition to being of extreme interest, also involve, as has already been pointed out, a rather complex analysis. What in my opinion it is important to do is to refer to certain fundamental principles in order to emphasise precise ethics and the rules of conduct to which researchers must adhere. If every form of human behaviour must be governed by rules, this is even more the case with those sciences which, in encountering life, find themselves faced with the dimension of the sacred.

The first principle to which I wish to refer is the Rabbinic maxim in the Talmud according to which 'to save a human life means to save the whole world'. From this observation we learn that the value of human life is infinite and that nothing in the creation, in terms of general and above all moral value, is above it. This idea about the sacredness of life draws its origin and its foundation from very many pages of the Bible and in particular from the account of the creation of man who was made in the image and likeness of God. There are a large number of implications which descend from this absolute principle. For example, the duty of a man to defend his own physical safety and to thus to attend to his own health. A medical doctor has the duty to act with all his science and knowledge on behalf of a sick person in order to achieve his or her recovery.

The Biblical commandment 'do

not remain inactive when faced with a danger to your neighbour' is normally interpreted by the Jewish masters as an invitation and an encouragement to engage in that scientific research which in the long term can be beneficial and useful for the health and the life of man. It is, however, implicit that its application must not involve a danger to the existence of man himself.

During its long and millennial history, Judaism has never had inferiority complexes towards scientific research and human progress. Man is recognised as having the capacity to advance and to reach very high levels, as indeed the eighth psalm observes: 'what is man that thou are mindful of him, and the son of man that thou dost care for him? Yet thou has made him little less than God *and dost crown him with glory and honour*'. And in relation to this point the Talmud explains that man is even superior to the heavenly beings because these last do not have freedom whereas man possesses the freedom to choose and is the only creature who is able to enter into dialogue with his Creator.

An expression of this intellectual and cultural superiority is to be found, according to the thought of the Bible, in the location of man within the creative process ever since the primordial period. That is to say in the capacity, in addition to the duty, of man to correct and to perfect those failings and imperfections that are to be found in the physical world. A significant expression of this approach is given in the famous reference in Rabbinic literature to the discussion between the Roman, Turnus Rufus, and the Jewish Rabbi, Akivà, on the qualities of human and divine works in order to establish which should be held to be superior.

The comparison between the seeds of grain (the work of the hands of God) and a freshly baked loaf of bread demonstrates the dimension of man and his positive role in the economy of the creation. Man collaborates with the Divinity and acts to achieve the perfection of the creation.

Man was created 'a little less than God' and is also the bearer of hope. Any medical doctor, researcher, theologian, person invested with responsibility, or man of faith and of good will, provides proof to God that the creation was worthwhile and that the healing of the sick and the alleviation of suffering is the finest act of faith that creatures can dedicate to their Creator.

After what has been said hitherto in this paper, it is clear that a person involved in research, and the use that he or she would like to made of the results of his or her research and studies, have an important role to play.

As has been observed, everything is in the hands of man, everything is conditioned by his moral conduct, by his fear of the Creator, by his respect for His will in relation to his relationships with his neighbour, that is to say man has been created in the image and likeness of God.

In the Biblical book Leviticus we find written 'let no one deceive their brother' and the text adds 'and you will fear your God because I am your God'. In explaining the relationship between the two parts of the text the great exegete of the Bible, Rashi, Rabbi Shelomò, the son of Izchak, added this note 'and you will fear your God' (translator's note: 'you' and 'your' in the second person singular), that is to say He who knows the thoughts of man. Everything that concerns the thoughts of man, which are known by the One who knows all the thoughts of man, should be the subject of the principle 'and you shall fear your God'.

The intelligence that God has given man allows man to overcome all the obstacles that stand in the way of scientific progress. At the same time, however, man must have the wisdom to prevent himself from being affected by the dizziness of his own discoveries and the results that he has achieved.

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6.2 The Islamic Perspective

In the complex and variegated field of bioethics the Islamic world is also confronted by the scientific discoveries and multiple challenges that are to be seen in biological and medical research, such as the research conducted on the human genome. The relationship between science, ethics and faith continues to be a subject of debate, discussion, study and research. In a broader sense, the relationship between religion and modernity is at the centre of the most thorny questions of the Islamic world. Muslim societies cannot flee from the problems of bioethics and the relationship between bioethics and the principles of Muslim ethics, which are founded on the articles of faith of the Islamic faith and the religious law of Islam.

It is important and necessary to underline the fact that nobody can withdraw from the questions posed by science. Science is constantly on the boil, it moves unceasingly, and it is a part of the human future of our times. Religions, and Islam is no exception to this, ask themselves about the ethical aspects, about suitable responses, and about the harmony between religious knowledge and scientific knowledge.

My intention in this paper is to expound certain essential aspects of the religious law of Islam, which is called *Shari'a*. In a certain sense they reflect the cardinal points of

the Islamic faith and the principles of Muslim ethics.

The following are the principal features of the religious law of Islam (*Shari'a*) that guide the human pathway, regulate the Islamic vision of the person, and establish the principles of Muslim ethics:

1. History and life within Muslim societies has always been shaped by the precepts, the values and the juridical system of the religious law of Islam, which is known in Arabic as *Shari'a*. For Muslims the religious law has divine origins, is based upon the texts of the Koran, and is elaborated by jurists (*fuqaha'*) according to Tradition and is constantly discussed by experts (*'ulama'*) during the course of history.

2. As the basis and foundation of the *Shari'a* we find the four 'roots of law' (*usul al-fiqh*) or sources from which have been drawn the principles of Muslim religious law. These sources are a) the Koran; b)Tradition (*Sunna*); c) the *'Ijma'* (the agreement of experts); and d) the *Qiyas* (analogical reasoning).

3. The institutional debates, the intellectual discussions, and common opinions on the interpretation and the application of the *Shari'a* continue to provoke great interest. Taking into account the Constitutions of independent states, there are three great theses in relation to: a) the *Shari'a* being the source of Muslim and civil law; b) the definition of the private and public areas where the *Shari'a* should be applied.

4. The role of the *Shari'a* in modern states with Muslim majorities continues to be one of the strong points of the institutional debate as to how to respond to two fundamental questions: a) how civil laws and religious laws can be harmonised in modern states; and b) what the relationship between religious authority and political power should be in nations with Muslim majorities.

5. It should be emphasised that the *Shari'a* is endowed with a notable capacity for adaptation to changes and varying situations. This fact is due to the absence of a supreme authority as the universal custodian of Muslim orthodoxy. The real problem is that of the institutional and legal guarantees granted to Muslim minorities in states with Muslim majorities.

6. The *Shari'a* is structured in a global system which is almost all-embracing. It governs family life (property, marriage, inheritance), bears upon social relations (education, defence, worship), and is an institutional guide in the public arena (laws of the state, justice, public morality, non-Muslims).

7. For Muslim law every human act finds its placement under the *Shari'a* and belongs to one of the following categories: a) obligatory (*fard*, *wajib*); b) recommended (*mandub*, *mustahabb*); c) free (*mubah*); d) ill-advised (*makruh*); and forbidden (*haram*).

The questions and issues of the subject of bioethics elaborated in the various states of the Muslim world almost always correspond to the positions elaborated by the various Islamic bodies, congresses and conferences (The League of the Muslim World, the Organisation of the Islamic Conference, the National committees of Legal Edicts – *fatawa*). The reports and the documents issued by the various biomedical bodies should be studied in this sense because contrasts and divergences between the positions of researchers and the positions of religious authorities are not excluded. One of the great difficulties is to find positions that are representative of the plural and vast community of Muslim faithful.

The most interesting aspect of the relationship between bioethics and religious law (*Shari'a*) is to observe that the questions of bioethics are pushing Islamic institutions towards an updating of Muslim law which is increasingly neglected or forgotten about by the positive law that is in force in individual Muslim states. In this sense it is necessary to bear in mind that every rule not expressed in the Koran or in the prophetic 'sayings' (*Hadith*) or not legitimately deduced from them is an 'innovation' (*bid'a*), a term that has become synonymous with heresy and heterodox change. When clear indications are lacking in Muslim tradition, different and at times opposing answers present themselves as being valid.

The debate on bioethics in the technologically advanced countries, with the accompanying 'frontier' proposals, rapidly spread because of the mass media and the means of communication. The debate that followed this has progressively induced an exploration and updating at three levels: a) the theoretical level; b) the deontological level; and c) the legislative level. From an Islamic point of view, the human person bears the impress of the creation, a fundamental concept in the link between faith and science and between ethical behaviour and juridical legislation. Human life, from birth until death, from conception to final resurrection, is guided by God the Creator. Thus the Muslim religion emphasises the sacrosanct aspect of human life. Human beings and the creation belong to God. In principle, man cannot on his own initiative modify, manipulate, change or interrupt the natural course of the divine order established by the Creator. From an Islamic point of view, the so-termed 'genetic changes' or 'genetic formulas' are against the harmony and the flow of life according to the principles of faith based on the revelation contained in the Koran and the collection of prophetic traditions. However, the aspect that appears to be of notable importance is the fact that the debate about bioethics and the human genome is leading Muslim societies and directing Islamic bodies towards a progressive revisiting of the juridical system of Muslim law under the guidance of Muslim jurists and experts. This is a laborious task, an arduous work, and amounts to a real challenge that involves the principles of Islamic faith on the one hand, and the discoveries of science, on the other.

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6.3 Hinduism and the Application of Knowledge about Human Genetics

Life is a strange phenomenon. It is full of unexpected miracles. A sudden quirk of fate, due to the last minute change in the programme of my Director General, gives me the opportunity to deliver a talk on "Hinduism and the Human Genome" at the eternal city of Vatican before an august audience of learned individuals. This very well relates to the Hindu philosophy of 'Prararbda Karma' by which each action is destined to take place because of the will of God, the omnipotent, the omnipresent. In fact, Hinduism is not a religion in the way the term is generally understood. It does not prescribe strict 'dos' and 'don'ts' but describes a 'Universal way of life' through the cosmic philosophy of Vedas and the great epics of Ramayana and Mahabharata. It is a vision and a way of life based upon an aspiration for light, enlightenment, to be ever moving towards the light and ever turning away from darkness, rejecting all that is darkness.[1] The meaning of life is transcending all darkness and ignorance. According to Hindu Dharma, no one can replace the role that one has to fulfill in God's creation at any given place and at any given point of time in a particular time-space context and should perform one's role in a meaningful manner without worrying about the results, since according to 'Karma' theory, beautifully narrated by Lord Krishna to Arjuna in Bhagavad Gita, 'Karma Yoga' is performance of action as an offering to the Lord and receiving its results without any expectation as His grace eliminates likes and dislikes and brings about a mind that is tranquil and open – a learning mind.[2] There will be no hesitation in doing what is to be done if one assimilates the essence of Gita. That is why Hinduism prescribes the duties to be performed by all in society which will take care of the rights of the others without giving any direct reference to the term 'Rights'. Hence Hinduism is a duty based religion, the Hindu Dharma.

Since the beginning of man's journey on earth, man has been trying to find answers to the question of what he really is, the perennial questions are what is life, when it begins and where it ends, what happens to the soul when it leaves the body after death, is there another world and does the soul remember its previous life when it enters into another body or is reborn in the form of life? According to the cosmic ideology of Hindus, the soul is nothing but the part and participle of the Cosmos or the Supreme consciousness with which it strives to unite through repeated processes of creation, growth and destruction which is considered as the ultimate truth or the ultimate reality. This theory of self-knowledge or self-realization is the essence of Advaita Vedanta/philosophy promoted by Adi Sankaracharya.[3] According to Adi Sankaracharya, a soul is a particle of cosmic energy which assumes the form of a physical body in which it presently resides. As the physical body disintegrates, the soul gets free and moves towards the Supreme abode to become one with the Centre of cosmic energy. During this journey it comes across other forces through a magnetic effect and may take a new life or new form and experience the joy, pain and sorrow of that physical body until a time comes when it escapes from this magnetic force and unites with the cosmic energy. This is explained by the concept of Trimurti that is Brahma, Vishnu and Mahesh – an attempt to explain the cosmic forms of energy. Brahma – a cosmic energy involved in creation of different worlds i.e. constellations, galaxies and the Milky Way for a certain duration of time. The process of action of holding together these worlds or for that matter a life for certain duration is attributed to Vishnu, the protector of life. The final disintegration and reintegration with the cosmic energy is denoted as Mahesh the Lord of the energy of destruction. The cosmic activities in the form of creation, protection and destruction have been described in Bhagavad Gita which in modern terms corresponds to the Big Bang theory of the creation of this world. With the progress of science and the quest to find answers to the true nature of nuclear energy, we are coming closer to the Hindu cosmic philosophy. The cosmic philosophy and principles allow a human being to grow beyond the limitations placed by the organic system. To understand the connection of the soul to the Universe or the philosophy that both are one and the same, one has to prepare one's mind to accept the unification of science external to science internal. The Upanishads, which are sectoral commentaries on the cosmic Hindu philosophy, had developed this great science of the human being in depth. Whether, it is the elitist higher Hinduism of the Vedantic tradition or the common democratic lesser Hinduism of the 'puranic' tradition, the ultimate truth is the belief that the purpose of life on this planet is to achieve the merger of the individual soul (atman) with the universal soul (Brahman

or Paramatman) to escape from the life cycle of births and rebirths which is determined by past actions (Prararbda). These basic concepts clearly explain the nuiances of human genetics and genomics based on the principles of the heredity and inheritance of traits and qualities. Modern genomic studies are able to prove that genes in a embryo are signatures of past life or in other words are hereditary in nature. A glance at the ancient scriptures and epics Ramayana and Mahabhartha indicates umpteen examples of scientific discoveries which are considered as new advances now, thereby proving the richness of scientific imagination and the ingeniousness of the vedic mind. The reincarnation, or in modern scientific terms, the cloning of a species can only be accepted if we accept the ideology of Vedanta that the soul in a physical body has a separate existence in totality and the physical characteristics are based on the genetic make-up resulting from man's past life. The references to various types of asexual reproduction in the ancient texts such as in vitro fertilization, genetic engineering, transplantation and cloning have been achieved by modern scientific advancements, but there are many more examples which are still beyond the scope of modern scientific discoveries. The way in which the two sons of Lord Shiva/Mahesh were begotten according to these texts seem to be examples of Somatic Cell Nuclear Transfer (SCNT) from ovum and sperm as in cloning technology, the latter still not achieved by modern scientists.

The birth of various 'asuras' (negative characters) though cloning technology gives a clear indication of the misuse of technology for wrong purposes as a lesson to humans, how any technology can cause harm instead of benefits if falls into the wrong hands. The story of 'Raktabij' a mythological demon whose every drop of blood produced another of his clone is one such example in Markendeya Purana.

The most interesting connectivity between the Hindu cosmic philosophy and the modern genomics is the symbol of OM. OM is the essence of life, it is the wisdom, which when once known leaves nothing to be realized (ॐ). The concept of OM has assumed predominance in the cosmic Hindu philosophy as it is projected as an all pervading force throughout the material world which is visible and in the invisible forces which are responsible for pro-creation of the different forms of the world including gross physical bodies, subtle bodies and causal bodies. In fact the concept of Trinity or Brahma, Vishnu and Mahesh are considered as the causal versions of OM.

It is said that OM in Hinduism

is similar to 'Amen' for Christians 'Amin' for muslims and 'Hum' for Buddhists. The chanting of OM and meditation on the symbol of OM is believed to bestow good health, prosperity, peace of mind to the spiritual aspirant. It is interesting to note the modern science is edging towards the era of Omics – Gen*om*ics, protein*om*ics, mitochondri*om*ics, transcript*om*ics, metabolin*om*ics etc. in the quest to unravel the mystery of life.[4]

Now coming to more mundane issues, looking at the burden of genetic disorders in the world and the resultant sufferings of those affected, it is imperative that scientists have a duty to come up with new technologies that will alleviate the sufferings of the humankind. However, as indicated in the ancient texts, the demons amongst us can misuse these technologies for destructive proposes rather than constructive activities as evidenced by some recent examples such as atomic bombing, sex selection technologies resulting in "Missing girls" in India etc. which demand adequate safeguards for the use of such technologies with potential harms. Hence, there is a need for appropriate guidelines for new technologies such as genetic engineering, assisted reproductive technologies, transplantation techniques, stem cell research, cloning etc. backed by adequate legislation. The challenges and opportunities with new technologies are tremendous. But this should be supported by proper control and oversight mechanisms. India is geared to face new technological innovations in the era of genomics with suitable guidelines from the Indian Council of Medical Research and Department of Biotechnology, which will be followed by adequate legislations. Any new technology should be welcomed by any religion if it has the potential to save humanity from sufferings. In this, Hinduism is a great support to scientific innovations of the right kind as it is more than a religion, it is an entire civilization, the story of man from the very beginning of time to find solutions to the problems of life, the story of the greatest of all adventures that of the human spirit trying to discover its true identity. Diversity and tolerance for all religions is the crux of Hinduism which is apply evidenced by the current political scenario in the country wherein an Italian Catholic is the President of the ruling party which has promoted a Sikh as the Prime Minister who was administered the oath of office by a Muslim President in a country which has an 82% Hindu population.

To conclude, the scientific in-

novations of the present time were already anticipated in the Vedic texts thousands of years back and any new invention can be welcomed which can offer hope to a suffering humanity for a better future, provided the freedom of scientific pursuits can be regulated to bring out only tangible benefits and not catastrophe or chaos in the Universe. That Hinduism will be a great supporter of modern science is a view that has been expressed by many religious leaders and scholars in the recent time.

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Notes

[1] SWAMI CHIDANANDA, *Ponder these truths*, Divine Life Society Publication, Rishikesh, 1995.
[2] SWAMI DAYANANDA, *The teaching of the Bhagavad Gita*, Vision Books, New Delhi 1989, 2003.
[3] PANDIT ATRE, *Soul@Universe.com*, Fusion Books, New Delhi 2004.
[4] Personal Communication of Dr. P.S. Chauhan, Mumbai.

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PUJYASRI CHANDRA SEKHARENDRA SARASVATI SWAMI, BHARTIYA VIDYA BHAVAN, *Hindu Dharma, The Universal way of life, Voice of the Guru,* Mumbai, 1996.
SWAMI SIVANANDA, *Ethics of Bhagavad Gita*, Divine Life Society, Rishikesh – 1957, 1995.

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6.4 Buddhism and the Human Genome

Counting down to the complete decoding of the human genome began with the 21st chromosome – its base pair sequence was published in *Nature Magazine* in May, 2000 by Japanese and German teams, and the whole base sequence was found by the International Human Genome Sequencing Consortium consisting of 2,800 researchers from the U.S.A., the United Kingdom, Japan, France, Germany and China. The overview version of all base pair sequences was published in Feburary, 2001, and a finished edition was published in October, 2004. The data was published so that anyone on Earth could use it freely. It became the intellectual property of the whole human race, and could not be patented by private companies. Scientists should not cling to their theories but instead systematically search for mistakes on their own. This is also the case in Buddhism, where attachment to oneself is abandoned. If scientific research is published so that anyone can use it, it can greatly contribute to mankind's welfare. However, its contribution is restricted when it is put under a patent. The recent tendency to patent medical research results is disappointing. The research by the International Human Genome Sequencing Consortium has helped science recover some of its integrity.

Science is not useful when discussing questions of values or ethics. It only determines whether something is true or false through experiments and observations. What can not be tested by experiments or observations does not belong to science. When we discuss refutable matters, we should use scientific knowledge. When we discuss matters which are not refutable, we should consider them in terms of humanism and with reference to the classics. We, mankind, critically analyze non-scientific matters through history and over time through literature. Works which are repeatedly selected become our classics. Some classic literature includes matters which are refutable. The value of the important part of the classic would not be diminished even if those refutable parts were updated with scientific knowledge. The central dogma of Buddhism is not to cling to oneself, so it could welcome the revision of the Buddhist classics by scientific knowledge. Interpreting Buddha's enlightenment from a genetic perspective, Buddha's realization freed him from the control of his genes. Animals are dominated by their genes and only repeat the cycle of birth, reproduction and death. However, humans wish for something beyond merely proliferating their genes. This differentiates humans from other animals. In order to transcend the animal's plight humans demand to be free from the restraint of their genes.

Buddha had three realizations one night. First, he realized he had had many former lives, which is called 'the wisdom concerning one's own reincarnation'. Later he realized other people had had former lives, which is called 'the wisdom concerning people's reincarnation'. In the last part of the night he realized how to become free from reincarnation, which is called 'the wisdom to eliminate pollution completely'. If reincarnation is reconsidered from a genetic perspective, what reincarnates is the genes. Buddha realized that all lives go through birth, reproduction and death infinitely, governed by genes and forced to reproduce genes. 'The wisdom to eliminate pollution completely' is expressed by Buddha as 'the fourfold noble truths', which are 'suffering', 'the cause of suffering', 'the extinction of suffering,' oth-

erwise known as Nirvana, and 'the path to Nirvana'. 'Suffering' comes from the Sanskrit word 'dukkha' which means, literally, 'to be denied what we desire'. Buddha said that there are eight sufferings. The first four are birth, aging, disease and death. The last suffering summarized all sufferings. It is the attachment to oneself. 'The cause of suffering' is passion, such as the passion for sex, the passion to live and the passion to die. These three passions correspond to the three elements of life in biology, those being; reproduction, dynamic equilibrium and death. These are the fundamental orders of genes for the proliferation of the genes themselves. 'The extinction of suffering' is the state of Nirvana where passions are extinguished and suffering, i.e. attachment to self, is also extinguished. This state brings freedom from the genes' restrictions. 'The path to Nirvana' is where passions are completely controlled. Attachment to the self is controlled by protesting against the genes' orders, and compassion for all others appears. Buddha showed, using a raft as a metaphor, that the essence of the doctrine was to leave attachments. A person having once crossed a river, will only be burdened by holding onto the raft that carried him. In this case, the raft is a metaphor for Buddhism itself! A Buddhist does not attach to Buddhism itself. Buddha said that what cannot be controlled according to desire is not one's own. We do not control our bodies as far as birth, aging, disease and dying are concerned. So, in order to control ourselves we must recognize that our bodies are not our own. This body does not belong to me so there is nothing that can be said to be mine or myself. If one considers oneself thus, one does not discriminate others from oneself.

In eighth-century China, the famous poet Li Bo teased an old monk who was meditating, and said "What are you doing?" "I am doing the yoga of Buddhism," he replied. "What is Buddhism?" asked Li Bo. "Commit no evil, do only good deeds, and in order to do so, purify ones heart by oneself; this is the teaching of all Buddhas. "Even a seven-year-old child knows that one should not do what is evil and should do what is good," said Li Bo. The monk replied, "Even a seven-year-old child knows it, still I cannot do it even in my seventies." Li Bo could not continue teasing the old Monk. As for the purification of

one's own heart, three poisons are traditionally mentioned. They are greed, anger and stupidity. Here stupidity does not mean the lack of knowledge. Instead it means not realizing that one's anger is not due to another's evil but due to the dissatisfaction of one's own greed. Medical ethics based on Buddha's teaching are as follows: "Commit no evil," which translates as not to harm patients; "Do only good deed," meaning to give priority to the welfare of a patient or a family; To "purify one's own heart," which corresponds with the principle of treating all patients fairly and equally. Buddha had compassion for all people without attachment to the self. So Buddhists affirm all religions equally allowing them to support a person's self-determination based on his own way of life.

The right-of-self-determination as a principle in modern ethics originates from "On Liberty" written by J. S. Mill. He pointed out the "tyranny of the majority" by discussing the way Socrates was treated in "Apologia". Socrates was accused of impiety for denying the gods recognized by the State, and of immorality, for corrupting youth through his teachings. Mill wrote, "Of these charges the tribunal, there is every ground for believing, honestly found him guilty, and condemned the man who probably of all then born had deserved best of mankind, to be put to death as a criminal." The court justly brought in a verdict of "Guilty" with the final numbers being 281 for guilty and 220 against. Knowing that he would not have been executed if he had only admitted to the charges in court, he did not do so. Because he chose death, there must have been something that was more important to him than his own life. If one's religion is anything one values beyond one's own life then Socrates' philosophy was such a religion to Socrates himself. It approves a religious liberty that is the ideal form of the right-of-self-determination. An adult with the ability of self-judgment can do anything with what belongs to him, as long as it does not harm others, even if it is a silly decision.

In a democratic society, public information must be published and kept transparent. As for personal information, privacy must be kept and an individual must be guaranteed the right of self-determination to handle it. Well, should a person who has had a gene examination be allowed to entrust to his self-determination whether the result of the gene diagnosis is told to his relatives or not? Does his gene belong to him only? It does not. One could argue that the gene is jointly owned by all family members who might have that same gene. Therefore, the right to handle the gene information is not left up to individual self-determination alone. Especially when the gene information reveals an illness which was inherited, the idea of self-determination shouldn't be used to deny that knowledge to family members who share that sick gene. Buddhist monks should make endless efforts to end attach-

ment to the self. They should also end being attached to Buddhism itself as is shown by the metaphor of the raft, and not bind others to Buddha's teaching alone. They should welcome other ways of life equally too, as acts of self-determination.

The novel titled "Kappa" was written in 1927 by the Japanese novelist Ryunosuke Akutagawa who is famous for having written "Rashoumon". Kappa is a creature from old Japanese tales that lives in a river. In Akutagawa's version, Kappa's world is a caricature of human society. In Kappa's society, the right to self-determination is perfectly guaranteed. For example, when Kappa's wife is pregnant, he calls to the baby in the mother's belly, as if he is using the mother's body as a telephone. He asks the baby whether it wants to be born or not. The baby in its mother's abdomen answers in a weak hesitating voice "I don't want to be born because, firstly, my father's heredity is awfully bad and..." The baby's right to self-determination is respected and it is not born in the end. As for humans, whether or not to be born cannot be determined by the baby itself. Buddha said that "birth" was the first suffering – suffering being those matters where we are denied what we desire. The suffering of birth is a changing aspect in comparison with that in Buddha's age.

Human beings who looked for freedom from the restraint of their genes now know the base sequences of the genetic code that laid their existence under restraint. Although we have found all the letters of this sentence, decoding the deep meaning is a problem for the future. Further research is necessary for the detailed elucidation of the genetic action that causes within us the passion to reproduce, to live or to die. Each new ethical problem which involves the research of human genes should be discussed under institutional review boards where members of the religious world are included. The ethical principles based on Buddhism are as described earlier – to control attachment to oneself and to wish for everyone's happiness, and in this specific case, to limit the tendency to obtain patents.

In closing, I would like to thank the International Human Genome Sequencing Consortium for its open disclosure of the human genome data. I hope, for the good of all people, that when patents are inappropriate for major medical research they will be blocked in the future as well. Thank you.

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JÁN ĎAČOK

7.Genetics and Post-modernity

Introduction

An illumination of the relationship between genetics and post-modernity certainly constitutes an original viewpoint. In order to have a better understanding of the trends of contemporary genetics, it appears to be very useful to present, to begin with, the cultural and anthropological characteristics of post-modern man. After this first step the conduct of post-modern man in the field of genetics will then be examined.

1. Post-modernity

The complex phenomenon of post-modernity has already been characterised by various thinkers. However there remain certain aspects that require clarification. The substantial nature of post-modern culture is expressed in an individualism that is possessive and anarchic in character and thus aims against every kind of authority. This kind of individualism is expressed in a series of negations: it is anti-family and anti-militarist, atheist and anti-clerical, against parties and against the state. These positions reflect an anthropological approach that places the absolute individual at its centre.[1] To summarise: post-modern or radical culture may be seen as an 'anti-culture'. I will now try to describe the most important characteristics of post-modern man.[2]

1. *Man is not a person but only an individual*. Post-modern culture has impoverished the idea of the person. This culture has abandoned the definitions of Boetius and St. Thomas Aquinas and favours a definition of a psychological or sociological kind, according to which only he or she who feels that he or she is a person or is recognised as such can be considered a person. In the place of 'strong' or ontological conceptions we encounter 'weak' functionalist and empiricist conceptions that only accept a set of certain activities or properties such as mental operations, self-awareness, sense perceptions, or the capacity to communicate or to make symbolic representations, as constituting the status of a person. There is thus opened up the path to dangerous approaches to man, amongst which we may list human cloning and the exploitation of the human genome. This position can lead to every form of manipulation and every form of treatment (even killing), as though man was an object,[3] because according to this radical culture by these routes one does not kill a person, one 'only' eliminates an individual. At the centre of radical humanism we encounter the 'absolute individual'[4] who makes up the core of individualism. This is very important in understanding post-modern man because it penetrates and influences his other characteristics as well.

2. *Man is substantially good*. Man is good by nature: his will, his reason, his senses, his instincts and his passions are good. His freedom is limited to obeying only itself and the laws that come from that freedom. Post-modern anthropology denies the reality of moral evil and rejects the supernatural order, and measures all things according to the absolute individual.[5]

3. *A full autonomy*. This is justified by the approach of post-modern philosophy which argues that there is no metaphysical order to being and that if this were to exist human intelligence is so weakened that it would not be able to recognise it. This forms that basis of what is a chaotic diversity in the ethical-moral field: the subject acts on the basis of what is good for him, of what he wants, and not of what is good in itself and for its own sake.[6]

4. *Pleasure not virtue is the basis of happiness*. Post-modern culture means by the concept of happiness the strengthening of every form of pleasure, and in a special way the full liberation of desires, the satisfaction of all needs, flight from suffering, enjoyment of life…This tendency is nourished first and foremost by the mass media.

5. *Only a contract and not the law is binding*. The absolute individual sees himself as the only point of reference. And thus all values have to be subordinated to this individual. Given that in the radical mentality the superiority of the common good over the indi-

vidual good is not accepted, radical man does not feel that he is bound by law. He feels, instead, that he is bound only by a contract.[7] He is, indeed, a believer in contracts. If a contract is advantageous for him, he makes it or renews it; if it does not have, or has already lost, its usefulness and advantage for him, he does not make it or he does not renew it.

6. *The lack of a historical memory*. Tradition and the historical memory are strongly rejected by post-modern culture.[8] Post-modern culture and society live only in the present and close themselves to the overall dimension of history that in itself connects the past with the present and also prepares for the future. However, other realities are connected with this, and in particular the reality to which V. Possenti refers: 'where there is no tradition there begins the time of poverty and the path towards inhumanity'.[9]

To summarise, if God disappears from the world scene, the world, too, becomes 'weak' – it is not understood as the creation of God but as an object, a thing; indeed, a depository of things. Such a world becomes exposed to man who through it can satisfy not only his needs but also his various desires and thus – from the perspective of an advantage – the world can be exploited in limitless way. A weakened world offers man the possibility of exercising his will to power. Man lives amidst an absence of God and an absence of truth about his own being. From here there springs his crisis of meaning and ethical-moral direction. Post-modern man has become 'weak' in an overall sense. He has lost the religious and sacred meaning of life, which, indeed, he sees in a depersonalised way, as mere matter to be analysed, to be produced, and also to be exploited.

2. Genetics

How can post-modernity and post-modern man be seen in the field of genetics? This will now be explored with reference to certain examples.

1. *Cloning and research on embryo stem cells*. Cloning that seeks the birth of child changes that child into a product. God's intention is for all babies to be conceived, born and embraced by the loving arms of their parents and seen as a gift. A cloned child, on the other hand, is produced in a sterile laboratory. A cloned being is created through a financial contribution and is the object of a quality control. This changes the approach in a radical way: a cloned baby is understood solely as an individual, indeed as a commodity, and is without any value or dignity.[10] Hence one can state that the post-modern approach in the sphere of genetics leads to a path towards the future bound up with many traps for the human race. Cloning and research on embryo stem cells may be seen as a bridge to very serious problems that deserve to be addressed in a very responsible way.[11]

2. *Genetic engineering and intervention on germinal cells*. Genetic engineering is divided into two principal groups according to the type of cell modification that is involved: (a) somatic genetic engineering and (b) germinal genetic engineering. The first modifies or replaces the genes only in the somatic cells and not in the germinal cells. Germinal genetic engineering modifies the genes in the oocytes, in the spermatozoa, in their precursors, in the zygote and in the embryo. It can also lead to a selection of genetic characteristics in a 'programmed baby' with the creation of a 'designer baby' who has the desired characteristics.[12] Intervention on germinal cells could become a very dangerous matter for the whole of mankind – the changes that are transmitted to future generations could change the human species. For these reasons, some thinkers are already referring to a 'post-human' nature when human identity is 'controlled' through a control of genetic inheritance.[13]

3. *The patenting of genes*. It is already possible to patent human genes and other human tissues, and this means 'holding as property' a part of our human nature. This means that a change in the way human nature is understood has already begun – human nature is understood as private property and no longer as something that belongs to everyone in the same way. The exploitation of genetic information will open the door to insurance companies and businessmen to implement different kinds of genetic discrimination.[14]

4. *Cybernetics*. This is defined as the science of systems of control and communication that in particular employs analogies between machines and the nervous systems of animals or man. In recent years notable advances have been made in this field, in particular in the neurosciences and in computerised technologies, and these allow a direct relationship between a nervous system of an animal or a human and electro-mechanical equipment. Examples of this are: memory chips implanted in the brain, cybernetic technolo-

gies in different fields, increased reality, etc.[15] They can help man in the struggle against various illnesses but they can also lead to a manipulation and exploitation of individuals and the whole of mankind.

5. *Nanotechnologies*. It is thought that these can make a major contribution to the development of the tools of cybernetics and to the modification of the human genome. Nanotechnologies are technologies involved in the engineering or manipulation of matter (and life) on the scale of a nanometre, that is to say a milliard part of a metre. One need only observe that a DNA molecule has a diameter of 2.3 nanometres. If the nanotechnologies involve such small distances one may well imagine that the structure of our bodies could be changed. Some people think that cybernetics and nanotechnologies are the instruments by which humanity will achieve 'technological immortality'. The tendency to extend the human lifespan through technological means, which is strongly supported by a growing philosophical and social movement, is known as 'transhumanism'.[16]

6. *Transhumanism and post-humanism*. Transhumanism is defined as 'a study of the means and the obstacles encountered by mankind in the employment of technological and rational instruments to become post-human, and the ethical questions that are involved. 'Post-human' is a term that refers to human beings that are much more developed that the humans of today'. We can become 'post-human beings' if 'we are able to govern our contemporary nature to achieve a higher level of quality and to extent our capacities in a radical way'.[17] 'Post-human beings' are no longer human beings because they have been so modified that they no longer represent the human species. The philosophical ideal of these two movements is that of a rebirth mixed up, however, with post-modern ethical relativism and post-modern ethical scepticism. From this concept of rebirth there comes a completely reductionist vision of human life. To this approach is added the replacement of God in a triumphal, utopian and arrogant way. Transhumanistic thought rejects the statement that nature is constant. In nature, and in particular in human nature, there is nothing sacred, worthy of respect, and deserving of protection against artificial changes. Thus one cannot reject criticism of the modification of nature to the effect that one is dealing with 'playing at God' or an example of supreme human pride.[18]

Conclusion

Some examples offered above confirm the strong influence of post-modernity on contemporary genetics: a lack of respect for man and his genetic inheritance by 'technological superman' who can allow himself to do almost everything. The practices mentioned above require a firm rejection that seeks the protection of man and blocks the process towards the 'abolition of man'. Post-modernity does not offer us the instruments by which to understand the human genome and respect for it in a better way. Indeed, it opens up the path to the exploitation of the human genetic inheritance. In order to admire, respect and protect the human genome it is necessary to look for solutions in other ways of thinking, and in particular in Christian thought. Christian thought teaches us that precisely because Jesus Christ accepted our nature there is no need to change and exploit human nature. This reality bestows upon human nature an impress of the highest dignity.

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Notes

[1] Cf. F. BOTTURI, *Desiderio e verit. Per una antropologia cristiana nell'et secolarizzata* (Milan, 1985), pp. 52-58.

[2] To this end I will follow as guidelines the thought of V. Possenti, I. Sanna, and G. Morra (*Il quarto uomo. Postmodernità o crisi della modernità*?, Rome, 1992, 1996[2]) and G. Bruni ('Dire Dio agli uomini d'oggi. Linee di discussione', in *Parlare di Dio all'uomo postmoderno*, edited by P. Poupard, Rome, 1994, pp. 23-35). For some aspects of postmodern spirituality see: T. MULDOON, 'Postmodern spirituality and the Ignatian fundamentum', in *The Way*, vol. 44, 2005, n. 1, pp. 88-100.

[3] Cf. I. SANNA, *L'antropologia cristiana tra modernità e postmodernità* (Brescia, 2001), pp. 365-372; see also F. BOTTURI, *Desiderio e verità*, pp. 112-127.

[4] Cf. V. POSSENTI, *Filosofia e società. Studi sui progetti etico-politici contemporanei* (Milan, 1983), p. 103.

[5] Cf. V. POSSENTI, *Filosofia e società*, pp. 103-104.

[6] Cf. I. SANNA, *L'antropologia cristiana tra modernità e postmodernità*, pp. 373-374.

[7] Cf. V. POSSENTI, *Filosofia e società*, pp. 121-124.

[8] V. Possenti emphasises the anti-historicist approach that is present in so clear a way in radical society: 'the radical individual does not believe or no longer believes in the rationality of history, and establishes between history and nature, and between culture and nature an often unbridgeable gap': V. POSSENTI, *Tra secolarizzazione e nuova cristianità* (Bologna, 1986), p. 72.

[9] Cf. V. POSSENTI, *Filosofia e società*, p. 126.

[10] Cf. CH.W. COLSON, 'Can We Prevent the 'Abolition of Man'?', in CH.W. Colson and N.M. de S. Cameron (eds.), *Human dignity in the Biotech Century* (InterVarsity Press, Downers Grove, Illinois 2004), p. 16.

[11] Cf. M.-L. LABAT, 'Human stem cells: scientific and ethical aspects', in *Ethics of human genetics. Challenges of the (Post) Genomic Era*, edited by J. Glasa (Charis-IMED Fdn., Bratislava, 2002), pp. 67-78.

[12] Cf. D.A. PRENTICE, 'The Biotech Revolution', in CH.W. Colson and N.M.de S. Cameron (eds.), *Human Dignity in the Biotech Century*, pp. 56-59; see also G. TRE RE, 'Ingegneria genetica', in *Dizionario di Bioetica*, edited by S. Leone and S. Privitera (Istituto Siciliano di Bioetica, Centro Editoriale Dehoniano, Acireale, Bologna, 1994), pp. 489-492; M.A. ROTHSTEIN (ed.), *Pharmacogenomics. Social, Ethical, and Clinical Dimensions* (Wiley-Liss, Hoboken, New Jersey, 2003).

[13] Cf. CH.W. COLSON, 'Can We Prevent the 'Abolition of Man'?', p. 19; see also L.M. BUCCI ,M. PAGANELLI , A. VENTURA , F. VENTURA, AND R. CELESTI: 'Osservazioni etiche e implicazioni medico-legali in materia di 'test genetici'', in *Medicina e Morale*, n. 4, 2005, pp. 799-810.

[14] Cf. CH.W. COLSON, 'Can We Prevent the 'Abolition of Man'?', p. 19.

[15] Cf. C.CH. HOOK, 'Techno sapiens', in CH.W. COLSON AND N.M. DE S. CAMERON (EDS.), *Human Dignity in the Biotech Century*, pp. 76-80.

[16] Cf. C.CH. HOOK, 'Techno sapiens', pp. 80-85.

[17] N. BOSTROM, 'What Is Transhumanism?', (2001) <*http://www.nickbostrom.com/old/transhumanism.html*>.

[18] Cf. C.CH. HOOK, 'Techno sapiens', pp. 85-87. At a practical level it is very significant that the government of the United States of America has embraced the 'ideals' of transhumanism and actively supports the development of transhuman technologies that seek to 'remake', 'improve' or 'regenerate' humanity, cf. C.CH. HOOK 'Techno sapiens', pp. 87-88.

Third Session

What Should Be Done?

PAUL POUPARD

1. Genetics and the New Culture

1. The historical pathway of genetic research, from Mendel (1822-1884) until today, has opened up new horizons for science and technology which, indeed, have been constantly advancing: a leap of quality in our knowledge about the structure of genes, in the application of the methods of recombinant DNA to the production of substances of a very high pharmacological and therapeutic importance, and in the diagnosis of genetic illnesses and the introduction of these new techniques into the field of experimental embryology.[1]

In addition, the great advances of genetics have opened up, and are continuing to expand, the areas of the genomic 'revolution', from which are expected notable benefits for mankind. Of fundamental importance here are the important applications that are developing in the field of medicine. It is an evident fact that over the last decades in particular the path of biomedicine has experienced an extraordinary development which has also been sustained by the advance of technology and communications and information technology which, indeed, have enormously increased the possibilities of intervening upon living things and in particular upon man. In addition, great advances have been achieved in the field of genetics, in the field of molecular biology, and in the field of transplants and the neurosciences. Each new discovery in the field of biomedicine, in the contemporary context, appears by now to be destined to produce 'cascade' effects and to open up new horizons at the level of the possibilities of diagnosing and treating pathologies that at the present time are incurable.

The acquisition of an increasing technical ability to intervene upon man, upon the other living beings and upon the environment, obtaining, moreover, increasingly effective and long lasting effects, requires from scientists and from society as a whole the taking on of responsibilities which become greater the greater the power of the intervention itself is shown to be. It follows from this that the experimental sciences, and thus also biogenetics, as instruments in the hands of man, are not enough on their own but require to be directed to specific ends and connected with the world of values. In the endeavour to search for, and to recognise, objective truth in genetic research and objective truth in the use of means and the ends to be achieved, a role of especial importance is played by scientists working in the fields of genetics and biomedicine. These scientists are called upon to work for the welfare and the health of human beings. Thus, every research activity in this field should always have as its ultimate end the overall good of man, and in the means that it uses it should fully respect the inalienable dignity of the person, the right to life, and the substantial physical integrity that are in every individual. For this reason, 'the Church respects and supports scientific research when it pursues an authentically humanistic direction, rejecting every form of exploitation or destruction of the human being and keeping itself free from slavery to political and economic interests'.[2]

From this one understands the importance of the ethics of genetic research which, in fact, have become increasingly developed and detailed, with the valuable and irreplaceable contribution of Christian thought which, indeed, has emphasised certain new questions and issues in the light of its original anthropological vision: respect for the person when he or she becomes the subject of research, especially in the case of experimentation that is not directly therapeutic, and emphasis on the close link that exists between science, society, and the person who is present in the entire process of research.

2. In the drawing up of an itinerary of genetic research that respects the real welfare of the person it is thus necessary to achieve a convergence in synergic fashion of the various disciplines that are involved with an integrating methodology that does justice to the complex constituent unity of the human being. The so-called triangular method, organised around three processes, is useful to this end: the exposition of genetic data; the investigation of the anthropological significance and the identification of the values at stake that such a fact involves; and the drawing up of ethical norms that can guide the conduct of those who work in this field, in a specific situation, according to the meanings and the values that have been previously identified.

The knowledge obtained through research in the field of genetics applied to man is very important and significant. The positive value of the knowledge about the genome of the human species, and in some cases about the genome of individuals, should be acknowledged. The positive character of the acquisition of genetic information is based not only upon the value of scientific knowledge as such but above all upon the possibility that it can work for the good of the person at the level of prevention, diagnosis and also the treatment of diseases with a genetic basis when this is practicable without disproportionate risks for the patients themselves. For that matter, the intrinsic link of the genome of man with the constitution of the person distinguishes it in essential terms from the genome of every other living species and constitutes the foundation of its inalienable dignity in relation to the human person himself or herself. For this reason, the human genome, because of the substantial unity of the body with the spirit, does not have only a biological significance – it is the bearer of an anthropological dignity which has its foundation in the spiritual soul that pervades the body and vivifies it.

3. Another aspect of great ethical cultural importance in the sphere of genetic research concerns the biotechnological developments that are now underway in the field of life and their consequences for persons and communities of persons. These developments give rise to questions and dilemmas which need new equilibriums and new forms of safety. These examples of progress now underway involve upheavals of meaning and action of such a kind that they constitute, and are considered in terms of, a real and authentic 'question' for society and the Church today.[3] In the presence of a 'question', Christians and the Christian community are called to approach matters not in the ordinary traditional ways of 'seeing, judging and acting' but in the radically new ways that are induced and solicited by *res novae*.

Life today, under the dominion of the growing biotechnological powers and their ambivalences, on the one hand, and of models of thinking and behaviour, on the other, is 'being questioned'. As such it constitutes an appeal to prophecy: the good of life is to be considered and adopted with the prophetic gaze and investment with which the Church discerns and takes responsibility for a 'question' in history. John Paul II did not hesitate to use the term 'mobilisation' in order to make us explicitly aware of what is at stake and of the commitment that is called for: 'what is generally called for is a general mobilisation of consciences and a united ethical effort to activate a great campaign in support of life'.[4]

4. The great progress that has been achieved in forty years of research in the field of human genetics, the achievements that have been made and the prospects that have been opened up, give rise to a dual question: we will know how to use this great progress and all the possibilities that have been opened up only on behalf of man, that is to say the exclusive good of man as a person and of mankind as society? In fact, is this extraordinary progress not perhaps already used – or at least in part used – against man? These are questions that impose themselves because both research and the applications of the results that are achieved when their objective is man cannot depart in their implementation from his particular state – a state that confers on him dignity and rights that cannot be neglected or violated without injuring the very ethical principles on which the real welfare of man and society are founded. But it is precisely in relation to these principles that agreement is absent, and from this there follows, almost necessarily, a strong tension that tends to divide thought and behaviour. The essential problems can be placed in three classes: problems connected with research seen as such; problems connected with its application at the level of diagnosis; and problems connected with its application at the level of treatment. Our approach has four principles as its foundation: (a). Science, that is to say the increasingly broad and deep knowledge that exists about the structure and the functions of the human genome, is an inestimable good. As such, that is to say as a complex of knowledge, of structures, of functions and of laws, it has a very great value in itself. (b). Engaging in science cannot depart from criteria for conduct that are based upon ethical reflection. The construction of science requires observation, analysis, hypothesising, and experimenting, and implies a personal contribution from the researcher-scientist, that is to say a responsible act. (c). Technology, that is to say the application of the knowledge acquired by science, is a great power of man which derives from his right to use the results of his research and his duty to translate them for the benefit of man himself. But the exercise of power, even more than engaging in research, also requires a norm rooted in the interiority of those who practice it. (d). The human person, his or her nature, and his or her consequent dignity, that is to say the integral reality that is objectively man, establishes the norm to be followed from his or her own interiority. It is this interiority, which forms one thing with man's 'biological' self but transcends it, that is called upon by man and points out to him what is right and what is good.[5]

The protagonist of this continual process of ethical orientation is unequivocally man himself. An inseparable unity of body and soul, the human person is characterised by his or her capacity to choose in freedom and responsibility the end of his or her actions and the means by which to achieve them. Man's urge to search for truth, which belongs to his very nature and his special vocation, finds indispensable help in

Truth itself, God, who comes to man, revealing to him His face through the Creation and more directly through Revelation. In this way God supports and sustains the efforts of human reason, allowing it to recognise the very many seeds of truth that are present in reality, and, finally, to enter into communion with the Truth itself that God is.

5. The very origin of mankind can today be studied through the evolution of the genome but the reality of the Creation, which is inscribed in the free act of love with which God gives being to the only creature that He wanted in His image and likeness, remains – beyond all scientific research – a requirement postulated by reason and an affirmation of divine revelation.

At the level of principle, therefore, ethical limits to knowledge of truth do not exist, that is to say there is no barrier beyond which man should not push in the efforts he makes at the level of knowledge. John Paul II thus defined man as 'the one who seeks the truth'.[6] There exist, instead, precise ethical limits to the way of acting of the man who seeks such truth because 'what is technically possible is not for that very reason morally admissible'.[7] It is therefore the ethical dimension of man, which he gives practical expression to through the judgements of his moral conscience that defines the existential goodness of his life.

Even more important is the drawing up of a set of criteria on the basis of which one may distinguish true personalism from false personalism. The first criterion is the affirmation of the substantiality of the human self-subject, otherwise one loses the vision of the irreducible uniqueness and singularity of the person and thus of his or her dignity. The second criterion is the affirmation of the capacity of the person to know a truth concerning the good and evil of man, independently of his interests, utility, individual tastes and preferences. The third criterion lies in the statement that the person is in himself or herself a whole that can never be used only as a means for an end that is held to be higher – *ratio partis contrariatur rationi personae*, as St. Thomas Aquinas declared. The fourth criterion consists in stating that the person is directed by his or her own nature towards 'communion' with other persons, that he or she is fulfilled in the gift of himself or herself, that is to say in love. The fifth and decisive criterion lies in the affirmation of the exclusive belonging of the person to God. This is the most profound criterion. The level of the dignity of the person is determined by his or her response to the question: 'before whom are we persons?', that is to say free subjects in a full sense. To be a person before God constitutes the person himself or herself in an infinite dignity. The sixth criterion, lastly, is the affirmation of the reasonableness of the choice of faith in Christ, God who made Himself man.[8]

6. A new culture with reference to the life of man, and in particular in the field of genetics, is thus necessary to become aware of the exact importance of the good at stake, to provoke and to keep alive within us awareness that actions and omissions in relation to life today lie beyond the sphere of the conscience and the behaviour of individuals. They flow over from the merely individual and private sphere in which they are thought about, decided upon, and carried out, and take the form and shape of thought, of mentalities, of the collective imagination, of public opinion, of the sociocultural habitat, of the prevalent ethos by which consciences are enveloped and strongly influenced. When a way of thinking and acting takes cultural form and density it acquires strength at the level of performatory strength, that is to say a strength to persuade in an immediate and direct way consciences in both directions: this applies to the very many examples of negligence and violence towards life which give rise to a counter-culture of death and this also applies to the defence and promotion of life. Thus we are all committed to the achievement of a cultural turning point, to promoting a new culture[9] of life. Indeed, if the Gospel of life does not walk with the legs of culture it cannot meet the challenge of the counter-culture of death. This is a challenge that is much more critical than the 'murdered dead' – in relation to which there spontaneously arises the unanimous indignation of people and the managers of mass communication – because it embraces all the abuses and crimes against life: from those accepted and tolerated with distracted and remissive tolerance to those not perceived as such or which are even perpetrated with cultural favour. In this way such actions lose the meaning of crimes and become accredited as legitimate expressions of individual freedom to be recognised and protected as real and authentic rights.

For example, the contemporary process of progressive globalisation that is investing the whole planet, whose consequences do not always appear to be positive in character, leads us to consider the need for fairness and justice in relation to genetic research from the point of view of its social, political and economic consequences as well. Given the increasing limits to resources to be allocated to the development of genetic and biomedical research, it becomes necessary to pay great attention to achieving a fair distribution of such resources amongst the various countries of the world, bearing strongly in mind the conditions of life in the various regions of the world and the emergency of the primary needs of the poorest and most

burdened populations. This means that all people should be assured the minimal conditions and means both to be able to take advantage of this research itself and to be able to develop and maintain an endogenous capacity for research.

The first task of men and women of culture, directed towards placing the gift of charity within history, lies in a achieving a broad-ranging discernment in order to understand the exact and real importance of how and to what extent the field of genetic research is questioned today and the cultural challenge to which it is subjected. Genetics, with its light and its darkness, its urgent and at times dramatic appeals, far from falling outside or at the margins of the role and the mission of the Church, is specifically at their centre. In dialogue with the world of science and research, the Church offers her own specific contribution because she participates in the destiny of humanity and of each individual person. Man in his unified and thus indivisible unity of body and soul[10] is the way of the Church.[11] On this theological and doctrinal foundation we men and women of faith and culture are called to address the 'question of man' and the great challenge that this represents, on both the biotechnological and the cultural fronts, so as to be able to understand and to respond, in the light of the Gospel, to the opportunities, the questions, and the issues of biotechnologies and contemporary culture.

7. We are thus induced to engage in an act of critical awareness that is able to intercept the challenges of the biotechnologies and culture in order to lay naked the delays, the examples of waste, and the insufficiencies of our role, but also, at the same time, to identify pathway and proposals.

a. There is an imbalance to be encountered in the attention paid to the problems of, and the need to find and provide practical answers to, the questions and conflicts brought about by the results and the opportunities offered by biotechnologies, and changed and changing cultural sensibilities. We are anxious to know, for example, about the licit character or otherwise of the use of stem cells, about whether or not surplus embryos can be used, about the extent to which a pill is abortion-inducing, about whether it is licit or otherwise to have recourse to a technique of fertilisation, about the legitimacy of, or our duty to engage in, a transplant operation, about the admissibility of an example of experimentation. But we do not take trouble to know the value of human life, the meaning of the life of an embryo, the truth of human generation, or the value of an act of manipulation. This leads us to look for a solution at the level of law but to neglect or to put of the formative aspect regarding questions of method, first and directive principles, and anthropological and bioethical models: knowledge, that is to say, that is at base or the root of the matter, and knowledge that is indispensable in providing a grounding to norms, in the creation of a *mens critica*, and in formulating or in helping to formulate prudent judgements of conscience. There is, to summarise, a polarisation – and this is what this imbalance consists of – around bioethical questions and issues rather than the foundations of the matter: this is an indicator of the shift from formation to information.

b. In addition one can observe a growing gap between the magisterium and the catechesis. In the presence of a bioethical magisterium of the Church – but also of a theological bioethics – which is abreast of the times and its challenges, there is a mediation at the level of catechesis and a translation at a pastoral-working level that are at times rather laboured. Ecclesial investment in terms of the proclaiming of the faith in this field needs some adjustments. There are admirable initiatives but they are the outcome of the sensitivity and the initiative of only some people. These are strongly committed people and groups but at times they feel a sense of loneliness, of being marginal, and of distance from the community. One perceives that the community is not the object of this pastoral care but rather some people who act more with reference, so to speak, to themselves than to the Church.

c. We could identify a third knot of problems in a sort of secularist prejudice by which culture in general, and bioethics, genetics and the sector of biotechnologies in particular, are strongly dominated. This cultural approach, involving as it does a prejudice, is based upon the preconception that the Church can only express dogmatic, confessional positions, which, as such, are rationally irrelevant and incommunicable. This is a major impediment which radically conditions not only cultural dialogue but also access to the major forums of mass communication. The difficulty lies in the axiomatic character of this position, the expression and the fruit of that lay pride that is nourished by the presumption that it has a monopoly over, and a contract on, reason. These are positions that wound intelligence more than faith and make dialogue and the preaching of the Gospel more arduous and patient.

d. The secularist prejudice, paradoxically, finds support – and this is another knot – in a fideism in relation to norms which leads interlocutors to think that Catholics have no arguments to give to themselves or to offer to others, that they profess moral norms as a creed, and that authority draws norms from a revelation and a faith that are alien to, and not attentive to, reason. This practical neglect of the relationship between faith and reason in the defence and promotion of scientific research and human life, and of genetics and the biotechnologies, gives rise to a kind of 'bioethical fideism' which debases the proclaiming of the Gospel, obstructs cultural dialogue, foments prejudice and does not provide a good service to the moral magisterium of the Church.

Connected with this aspect, emphasis should be laid on the problem of the inadequacy of training at the level of the ethics and culture of dialogue between the Gospel, science and reason, and between faith and scientific research. The result is that the Gospel and the ethics of life remain at the margins. This is a situation that is at the root of voids at the level of grounding, with a consequent ignorance about basic and decisive, central and critical, knowledge, which, indeed, is indispensable in measuring up to questions, provocations and conflicts of conscience with the people who ask us questions. The risk that is run is that of drawing and depending upon oth-

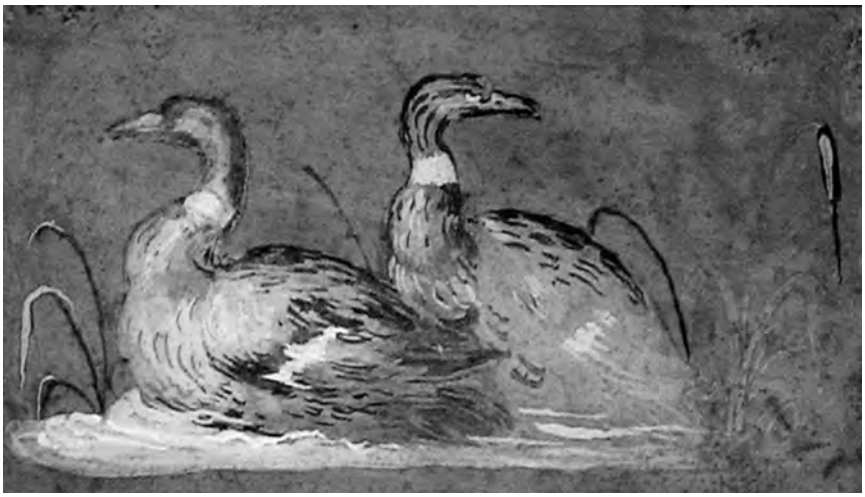
er 'cultural and ethical agencies', which are certainly not absent, especially on the great stage of communication and persuasion of the mass media.[12]

8. After identifying some problematic knots, I would now like to outline certain pathways that can be travelled to overcome difficulties, and which provide effective and possible responsibilities as regards a cultural undertaking of science and faith.

a. To begin anew from the Gospel of life and thus from the evangelising, missionary and ministerial value of the commitment to life on the part of men and women of culture and science as all of us are. A charge and a mission to be lived not according to a dichotomic and spiritualistic vision of life but in line with a profoundly unitary vision, and this in order not to separate the spirit from the mental-physical. Thus life is served in conformity with the fullness of its truth. Human life is a single and unique good in every dimension, stage and condition of its existence, and is thus indivisible and irreducible in its value. We are called to serve life on all the fronts of its being in the world and of its being today – made a problem of, disowned and offended as it is: on the front of warlike violence as on the front of crime, on the front of exploitation as on that of abortion, on the front of marginaliation as on that of euthanasia, on the front of disproportionate risk as on that of banalisation, and on the front of exaggerated treatment as on that of luxury.

b. To bring out the anthropological value of the Gospel of life. The centring of the truth and the value of life on the Gospel enlarges the field of intelligence. Indeed, the Gospel of life in opening up to the knowledge of the faith does not reduce or close that of reason, but solicits it, implies it and provokes it. Hence the universal value of the Gospel of life: it is not exclusively for believers – it is for everyone; it has a persuasive and profound echo in the heart of every person, both believers and also non-believers, because while it infinitely exceeds expectations it also corresponds to them in a surprising way. The Gospel of life, in fact, contains within itself what human experience and reason themselves say about the value of life, and completes it. It is a place of encounter for everyone in a multicultural, multireligious and pluralist society. Thus it is important to emphasise the anthropological reasons that form the basis for respect for every human life and become a place of cultural dialogue and the inculturation of the Gospel.

c. To stimulate attention and sensitivity towards the methodological correctness of the bioethical teaching of the Church, a teaching that is open to the truth of life on all the fronts of knowledge, not only those of the interpretational kind of theology and of philosophy and those of a normative character of ethics, but also, and even prior to them, on the investigative fronts of the biomedical sciences. To bring out the scansion



of *bios-logos-axios-deon-nomos-telos* in the drawing up of the teaching of the Church. To reveal how at the basis of this composition attention is paid to *bios* and thus to the contributions of the biological and medical sciences, in which intelligence illuminated by faith reads a *logos*, that is to say a profound meaning, which is an expression in its turn of an *axios*, that is to say of a value, in itself the bearer of a *deon* (a task), which takes form in *nomos* (law), with a view to realising the *telos* (end) of a person.

In this way one can face up to the great cultural challenge, that is to say the value of life at all its stages and in all its manifestations. Indeed, the temptation and peril we face today involve sliding into, and giving way to, a culture of the relative.[13] In certain situations the temptation is very great, as in the case of the manipulation of the genetic inheritance of a person, the use for therapeutic purposes of surplus embryos, of malformations in foetuses, of pregnancies caused by rape, of individuals in a persistent vegetal state or affected by grave mental-physical handicaps, and of the terminally ill. In a utilitarian and at times emotivist culture 'the circle is not squared', and thus life, too, is placed in the calculation of goods to enjoy and it is subjected to other preferences.

Life undergoes a *vulnus* and everything becomes relative to me;[14] it is subjectivised to my way of seeing, thinking and judging. Truth is surrogated by opinion, the value of feeling, the freedom of free will. This, in a utilitarian and relativistic culture, requires prophetic ardour and intellectual audacity in order to provoke and motivate in believers and non-believers recognition of the value of scientific research that is at the service of am. And it is of fundamental importance to proclaim this, both culturally and pastorally, to people who think *etsi Deus non daretur*, specifically along these anthropological co-ordinates of the Gospel of life. Otherwise one risks suffocation, after amnesia.

d. To invest first of all in the training of trainers, with care being taken not to limit this training to the many, impelling and complex questions that come to us and challenge us on the terrain of practice and event, but to learn the message, the language and the logic of life, and to organise the training courses around life. In

order to have a solid grounding that is able to address and to settle all the questions and issues involved, we need to achieve that grounding beginning with premises and strong bases at the level of methods, values, first and directive principles, the drawing up of norms, and philosophical, Biblical and theological anthropology.

e. To proclaim hope and cultivate virtue. The challenges to culture and in particular to genetic science and biomedicine today involve all researchers and scientists, lecturers and pastors, because such undertakings do not easily encounter a broad consensus and cultural favour. Of decisive importance here is the virtue of hope. Intelligence and faith are not sufficient – we need hope. Without this 'passion of the possible' the spring of truth and of love 'despite everything' disappear. We need a pastoral conversion to hope and virtue, to this disposition of the mind and the heart to know and love the True, the Good, and the Beautiful. Indeed, the Gospel and the culture of life are proclaimed and promoted, put down roots and bear fruit, because of the harmonies and the affections cultivated by virtue, in the open spaces of hope.

9. Thus the work of all of you, men and women dedicated to research, science and culture, takes on a completely new importance in this era which is marked by the development of science and biotechnological research. Great responsibility towards society and humanity is also made necessary, above all in relation to certain crucial questions: a. the clarification of the relationship between science and ethics in the biomedical field – the epistemological problem; b. secondly, it must be asked to which bioethics one must refer – the question of foundations; c. the urgent need for a cultural and political action so that law and laws take on the fundamental values that touch upon the defence of life.[15] Indeed, one has the sensation that a power that has never been greater is generating not greater security as regards living but, on the contrary, greater insecurity and ungovernable disorder, almost a sort of disquiet felt by omnipotent man. He perceives the real possibility of altering his own identity to the point of making it unrecognisable and thus to destroying it. We know how to come together to place this scientific and cultural legacy at the service of the true progress of mankind. The task as it presents itself to us is enormous. Indeed, some could define it as being utopian. Instead, I wish to encourage trust in man, against all the temptations of fatalism, paralysing passivity, and moral defeatism, This is a commitment, an appointment with history, that our intellectual and spiritual genius can address through a new mobilisation of the talents and energies of each person and by exploiting all the technical and cultural resources that are available to us.

We possess extraordinary economic and scientific resources and resources at the level of research thanks to which it is possible to give a decisive impulse to the human family, avoiding amongst other negative tendencies the temptation of biotechnological development for its own sake as though one should always do that which is scientifically and technically possible.

A second negative tendency to be avoided is that of making technological development a servant of economic utility in conformity with the logic of profit or endless economic expansion, thereby creating situations of advantage for some people and leaving others in overall poverty, without being concerned about the true good of humanity, and making of scientific research, and genetics in particular, an instrument at the service of 'having' to the detriment of 'being'.

All of you, men and women of culture, research and science, enjoy immense moral credibility for intervening in centres of decision-making, whether they are private or public, and for influencing the policies of countries. Employing all honest and effective means, make a total vision of man and a culture of integral humanism prevail in which science and research find their justification in serving man and mankind! Men and women of science, in the world of research and in universities, in cultural centres and in laboratories, be strongly committed to studying and proposing answers to the questions and the needs of society! To achieve all of this, in addition to technological capacities, we need elevated inspiration, courageous motivation, and great trust animated by hope in the future of man and his dignity.

H. Em. Cardinal PAUL POUPARD
President of the Pontifical Council for Culture, the Holy See

Notes

1. Cf. SERRA A., 'La "Nuova Genetica" Attualità, Prospettive, Problemi', in AA. VV., *Medicina e genetica verso il futuro* – (Questioni Aperte - Quaderni dell'Istituto Accademico di Roma, L'Aquila-Rome, 1986), pp. 9-12.

2. JOHN PAUL II , 'Address to those Taking Part in the IX General Assembly of the Pontifical Academy for Life', 24 February 2003, n. 4.

3. COZZOLI M., 'L'impegno della Chiesa per promuovere una cultura della vita', in SEGRETERIA GENERALE DELLA CEI (ed.), *Coeso di aggiornamento su temi di bioetica* (Rome, 2003), pp. 187-207.

4. JOHN PAUL II, *Evangelium vitae*, 25 March 1995, n. 95.

5. Cf. SERRA A., '*La nuova genetica, per l'uomo o contro l'uomo?*', in MAZZONI A. (ed.), *A sua immagine e somiglianza? Il volto dell'uomo alle soglie del 2000. Un approccio bioetico* (Rome, 1997), pp. 109-113.

6. JOHN PAUL II, *Fides et Ratio*, 14 September 1998, n. 28.

7. CONGREGATION FOR THE DOCTRINE OF THE FAITH, *Donum vitae*, 22 February 1987, n. 4.

8. Cf. CAFARRA C., 'La persona umana: aspetti teologici', in MAZZONI A. (ed.), *Op. cit.*, pp. 76-90.

9. JOHN PAUL II, 'Address to the Members of the Pontifical Council for Culture', 12 January 1990, n. 2.

10. '*Corpore et anima unus*' declares *Gaudium et spes*, n. 14.

11. JOHN PAUL II, *Redemptor hominis*, 4 March 1979, n. 14.

12. PONTIFICAL COUNCIL FOR CULTURE, *Per una pas*

torale della Cultura (Vatican City, 1999), n. 9.

13. BENEDICT XVI, 'Address at the Opening of the Ecclesial Conference of the Diocese of Rome on the Christian Family and the Christian Community', 6 June 2005. The following passage is of primary significance: 'Today an obstacle that is particularly insidious in relation to the work of education is the massive presence in our society and our culture of that relativism which, in not recognising anything as definitive, leaves as the final measurement only one's own self with its desires, and beneath the appearance of freedom it becomes for each person a prison because it separates one person from another, putting each person in a condition of being closed up within their own 'ego'. Within such a relativistic horizon, true education without the light of truth is not, therefore, possible; sooner or later each person, in fact, is condemned to doubt the very goodness of his or her life and the relationships that go to make it up, of the validity of his or her commitment to build something with others in common'. See also JOHN PAUL II, *Evangelium vitae*, 25 March 1995, n. 70.

14. Cf. DE ROSA G., 'Il relativismo moderno', *La Civiltà cattolica* vol. III/3726, pp. 455-468.

15. Cf. SGRECCIA E., 'Attualità delle problematiche bioetiche e contesto culturale', in *Corso di aggiornamento su temi di bioetica* (Atti a cura della Segreteria generale della CEI, 14 – 16 novembre 2001), pp. 5-20.

ANGELO SCOLA

2. A Pastoral Vision of Genetic Research

1. A Definition of the Concept of 'Pastoral Care'

In order to address in a adequate way the subject that has been assigned to me within the pathway of investigation of this conference – which has witnessed you involved in the analysis of the contemporary status of genetic research in the light, as well, of Christian revelation in the context of other worldviews and cultural tendencies – it seems to me to be of especial importance to clarify first of all what one should understand by the term 'pastoral care'. Such a premise will allow us to reflect on this subject beginning with one of the fundamental contributions – in the wake of the prophetic intuition of the Blessed John XXII – that the Second Vatican Council offered to the Church and thus to theology.

The pastoral character that characterises the proposals of Jesus Christ to the human family is well expressed in the mission itself of the Church – 'God our Saviour, who desires all men to be saved and to come to the knowledge of the truth' (1 Tim 2:4). The Second Vatican Council and with it the whole of the post-council Magisterium sought – in profound continuity with all Holy Scripture and Tradition – to place the salvific nature of the Church in the foreground by emphasising her pastoral character.

The salvific-sacramental key to pastoral care has allowed a special investigation of the category of the *signs of the times*. This could find and further and urgently important ontological and theological development in reflection on the sacramental value of the *circumstances* and *relationships* that each day involve the freedom – which is always historically located – of man. Such an approach, amongst other things, makes dialogue on a broad front effective: from ecumenism to the relationship with the other religions, from deeply-felt dialogue with the men of the so-called secular world and on to the eloquent witness of charity. From a making explicit of the pastoral dimension of the Christian fact springs a conception of the most immediate ecclesial action that is linked to the direct witness of the profound correspondence of Jesus Christ to the yearning for salvation that is present in the heart of every man and of the human community.

In this perspective the pertinence of thought about the *pastoral vision of genetic research* is evident. Such an exploration seeks to demonstrate that the questions that spring from genetic research – a privileged circumstance (a sign of the times) of culture and society today – intercept the mission of the Church. Or, in other terms, how the anthropological questions that are inevitably raised by scientific research in this field require, and can find, a suitable answer in the message of Jesus Christ, the 'complete figure' of the human (cf. *Gaudium et spes*, 22).

2. Contemporary Genetic Research

In order to direct our gaze, in the light of the salvific-sacramental mission of the Church, towards the reality of contemporary genetic research, we should first of all ask ourselves what genetic research itself is today. With this concern in mind I drew up the notes that I here propose having drawn on the help of a biologist.[1]

This question immediately raises another, a question which is run through with dialectical tensions that at times are also sharp: should the whole of the high-temperature front of the contemporary advance of biological knowledge be attributed to 'genetic' research? We cannot ignore, in fact, that this line is broadly followed by most of the information provided by the mass media, which also ascribe to 'genetic research' discoveries that are not strictly to be attributed to it, or selects only the 'genetic' side of such discoveries. The risk, therefore, is to pose the questions that most interest us not always to the right interlocutors, falling in this way into a unilateral approach which privileges the strictly genetic point of view but loses sight of a more overall perspective. On the other hand, it goes beyond the specific concern of this international conference to address all the emerging questions and issues of the biological field. For this reason, I will confine myself to addressing – obviously from the point of view of a 'lay person' as regards the genetic-biological sciences – only some of these high-temperature questions of genetic research, emphasising the contribution of other disciplinary approaches as well above all when these approaches, beginning with different assumptions, modify the interpretation of results and consequences.

To say genetic research today means to say something that is very different from what was meant at the beginning of the 1980s and the 1990s. Indeed, thanks to the refining and the automation of the techniques of the sequencing of DNA –. including the ancillary techniques that involve the amplification of segments of DNA and the bio-information technologies as well – in the space of a few years the sequences of entire genomes have become available. As is well known, the first completed sequence of the human genome goes back to June 2000. At the present time, more than two hundred and twenty genomes of micro-organisms have been sequenced as well as about twenty genomes of higher organisms. In addition, increasingly innovative methods of sequencing based on chemical reactions that are especially complex are being applied, the use of which lead people to posit

that within five years' time it will be possible to sequence the entire genome of an individual man at a cost of a little more than a thousand American dollars.[2] In addition, the time needed to carry out a sequencing will be especially reduced by making this kind of analysis, in terms of the time that is envisaged for its completion, similar to that of a complex biochemical analysis of the present time – a few days, to be precise. Thus every individual will be able to have an identity card of his or her own genes at a relatively low cost and a cost that is destined to grow even lower with the passing of time. It is evident that this process will complete one of the principal objectives of 'classic' genetics – detailed knowledge about the genome. A new epoch is being opened up, which not by accident has been defined as the *post-genome epoch*, an epoch characterised by the availability to all biologists of the information contained in the genome. The return to old questions and problems and the emergence of new ones flow from this.

3. Some Significant Questions

How is the mission of the Church involved by these questions and problems which are certainly of ancient date but which today have acquired a power of newness that is often explosive? A careful observer will not miss the difficult fact that has always afflicted every social practice and theory and which has become more acute during our era. I am referring here to the great difficulty that is encountered in creating a *consensus of experience and culture* upon the basis of the fundamental criteria of social life itself, including ethical assessment of a delicate kind which we cannot forgo. This grave handicap often reaches the point of impeding individuals and peoples from identifying those causes which deserve to be embraced at the level of personal life and public life. The reason for this state of affairs can perhaps be traced back to a statement to be found in a famous study by Franz von Kutschera: ethics alone are not sufficient to animate the wishes of man, even if 'mediation between moral interest and needs is the central problem of ethics'.[3] How should this state of affairs be tackled? Only by recognising that in order to lead freedom to embrace its duty (ethics) – in the field of genetic research as well – it is necessary to demonstrate the appeal, the advisability, of new *lifestyles*. But, as has often been emphasised during the history of the West, 'style is the man'. Thus only a suitable anthropological proposal is able to move the freedom of individuals and to push it, through the intermediary bodies, into the virtuous circle of the *good life* at both a personal and a social level. Thus *even before ethics, genetic research requires anthropology*. Genetic research, in fact, introduces a conception of man and the social community. This is the first and most important pre-condition for a pertinent pastoral vision of genetic research. Can we find an objective confirmation of this statement in the emerging questions and issues connected with the *human genome*? It seems to me that an answer in the affirmative is possible. Let us now consider certain examples of this.

a. Genotype-Phenotype

The new 'era' of genetic research poses anew an ancient question, newly arraigned in the light of the knowledge about genomes: what relationship is there between a genome and an organism (the genotype/phenotype relationship)? In the undertaking of answering this question there participate not only geneticists but many other biologists (biochemists, molecular biologists, physiologists, embryologists, zoologists…) who can now address the genome-organism relationship with the information contained in the genome. As is inevitably the case, understanding of the genotype/phenotype relationship is influenced by the original training of the various researchers involved. The classic genetic approach uses information about genomes to deduce from it the link between the genotype and the phenotype: no longer an individual gene/individual characteristic kind of relationship but that of the whole genome and the whole organism. It seems to me that the principal methodological approaches are: the sequencing of the genomes (or parts of them) of many individuals of the same species,[4] and a comparison of the variability at the level of the genome with the variability of the phenotype, from the simplest characteristic to the most complex. At the base of this approach we encounter the idea that the phenotype value of each characteristic of an individual is determined by the action of a few or many genetic factors, each of which contributes in a varyingly determining way to defining its value. This conception reflects the idea of a genome divided up into small units (the classic idea of 'modern synthesis') from which it follows that the information needed to describe the whole organism will be accessible once the function of each unit has been learned. A suitable method for obtaining this knowledge is the analysis of the covariance between genomes and characteristics (in other words, if the variation of a specific character, for example, height, corresponds to variations in certain particular genome sequences, it is probable that these sequences are at the basis of this characteristic). This kind of approach could, among other things, revolutionise the normal therapeutic approach to many kinds of common pathologies such as heart disease, diabetes, osteoporosis…It is believed, in fact, that these kinds of pathologies are not caused by an alteration in a single gene but that in our gene sequences and in the variability of the small units referred to above there are inscribed higher or lower levels of susceptibility to the development of such pathologies. However hitherto these notions have continued to be rather general in character and with few indications at the level of prevention because further research on the covariance of genomes is required, above all taking into account the specific character of different ethnic groups. However, they will be extremely relevant from the point of view of eugenic measures. This is a

consequence that is of decisive importance for pastoral care.

Another approach to the question, which is different from the genetic one, is that pursued by biochemists, molecular biologists, physiologists, and specialists in bio-information technology, through the development of new technologies which are commonly called 'omics'. For example 'functional genomics' has developed technologies to engage in simultaneous analysis of how the expression of the entire genome of an individual varies after a specific condition (stage of development, exposure to environmental conditions, the administration of pharmaceuticals…).[5] These technologies produced an avalanche of information that in the end stimulated the birth of a new specialisation – 'system biology'. The aim of this discipline is to establish the predictive value of the genotype as regards the phenotype by providing an overall picture, through theoretical approaches and approaches involving bio-information technology and models, of all the modifications that take place in the individual at all levels (the genetic and the epigenetic levels, that is to say). One question still in the ring is the following: to what extent is the living organism totally described by the genetic level and to what extent is it the epigenetic level that counts?

The substantial difference between the two approaches to the genotype/phenotype problem is evident: in the genetic approach what is between the genotype and the phenotype, that is to say how a specific genotype finally expresses itself in a specific phenotype, is not of interest. The postulate is implicitly adopted that it is the genotype which dominates whatever the case ('genetic essentialism') and independently of the path of expression. The second approach, on the other hand, privileges the study of 'what is between the genotype and the phenotype', and thus how the expression of the genome is regulated, and how the genes and the products of genes etc. interact with each other. Here the idea is implicit that epigenetic factors are of relevance in determining the 'phenotype value': the culmination of this is 'system biology' which explicitly states that in an individual 'the whole holds', that is to say that the parts do not explain the whole.

The important theoretical consequences and the consequences at the level of application of the two approaches may be perceived at various levels. I will now consider two: the predictive diagnosis of a predisposition to illnesses and socio-genomics. As regards predictive diagnosis, which is of great relevance to health, one should state that it is based on the assumption that the aetiology of many illnesses is the result of genetic, factors, environmental factors and the interaction between the genotype and the environment. One example of such interaction is exposure to the sun (an environmental factor) and such cancer is more frequently the cause of skin cancer in individuals with light skin than with dark skin – skin colour is a genetic fact. The objective is to isolate the genetic component by identifying the gene or more commonly the complex of genes that is as the base of this predisposition. The method is based upon the fact the human genome is different from one individual to another only by a small fraction (less than 0.1%): it is thus possible to characterise the genome of an individual on the basis of the presence of a specific set of variants (haplotypes). At this point one has to see if the frequency of some haplotypes is greater in individuals than are the carriers of a certain illness as compared to a homogenous group of healthy individuals. In the case of some illnesses the association with particular genes has been known about for some time (Mediterranean anaemia, haemophilia etc.); in other cases there are good 'candidate genes', and in yet others genome-wide association studies are underway that are principally focussed on the categorisation at the level of haplotypes of the human species.[6]

The problems that such research generates are many in number: obviously there are the problems of 'genetic counselling', genetic discrimination, neonatal screening, etc. From a pastoral point of view, it is important emphasise two problems in particular. The first concerns the shift – which is fostered by this kind of research – from ethics that places the individual person at the centre of things to ethics that places the (family, social. etc.) group at the centre. The second aspect is the stress that is inevitably placed by this research on genetic determinism (the genes are the essence of the person – 'genetic essentialism'). In this particular case, however, it is of decisive importance to ask oneself what the level of reliability of the predictive diagnosis actually is. Here there exist two types of problems: the first is linked to the fact that predisposition to a certain illness frequently depends not so much on the presence of one or more gene variants of the genome but rather on the interaction between various genes (the technical term is 'hepistasis') and the methods of association studies do not bring out the hepistasis; the second is a result of the fact that in the case of very many illnesses the environmental factor if absolutely dominant.[7] The consequences of these limitations on the application of predictive diagnosis are evident.

The term 'sociogenomics' refers to the latest development in sociobiology. It holds that the primary function of an organism is to reproduce its own genes and to constitute a provisional vehicle for those genes (the concept of the 'selfish gene'[8]). As a consequence the social organisation of individuals, too, must meet this objective and thus genes must exist that control social organisation. The aim of sociogenomics is to understand social life at the level of its genetic determinants or, in other terms, to describe the molecular bases of the social.[9] The methods that it utilises involve the evidence that has hitherto been available on the genetic bases of behaviour in experimental models[10] together with the genomic approach that has been described above for predictive diagnosis applied to experimental groups (animals) with contrasting social behaviour (for example the presence of a hierarchy of dominance versus its absence). This thesis argues as follows: if the social

has a genetic basis, associations must be perceivable at the level of the entire genome between particular haplotypes and particular forms of social behaviour. It is clear that the methodological objections raised in relation to predictive diagnosis are equally valid in this area as well – if not, indeed, even more valid. However, here another element should be added. It is clear that one of the objectives of this research is to obtain confirmation at the level of the human species of possible associations between the genotype and social behaviour such as are to be found in animal models. In these models, however, forms of social behaviour are extremely rigid, they are stereotypical, and they are perpetuated with very few variations during the course of the subsequent generations. In the human species, in different fashion, forms of social behaviour are extremely variable and above all change in a very rapid way with the generations to the point that it is unthinkable that they are conditioned by corresponding genomic variations that become established within the population. This simple fact should lead us not to underestimate the qualitative leap, which has always been recognised in anthropology, between the animal kingdom and the human kingdom. Here a decisive area is opened up for present and future pastoral action.

b. Evolutionary Theories

The principal reference currently available to the theories that endeavour to provide an answer to the nature of the forces and mechanisms that guide the evolution of living organisms is still the 'modern synthesis'.[11] It attributes the origins in natural variability observed by Darwin to mutations at the level of the DNA and describes the action of Darwinian natural selection with the methods of population genetics. By now this theory has many failings but somewhat because it is very 'accommodating', and somewhat because real and authentic alternative syntheses are lacking, it continues to be the theory of reference from a conceptual point of view.

Amongst the basic concepts of the theory one of the crucial points is that the probability that a particular mutation will take place rather than another is completely independent of its phenotype consequences. For this reason, the mutations (and thus the genetic variability) are said to be a matter of chance and natural selection is held to choose from the resulting phenotypes that are most 'adapt' (see 'chance and necessity' of Monod). This assumption is very present in Darwin in the metaphor of the architect: if an architect were to build a comfortable and beautiful edifice without choosing worked stones but by taking curved stones for the arches, long stones for the columns and flat stones for the roof that he had gathered from the bottom of a precipice where they had fallen we would admire his ability and we would see him as the principal force at work in the construction. Now, the fragments of rock, however indispensable they may be to the architect as regards his building, have the same relationship as do the fluctuating variations of every organised being in relation to the varied and admirable conformations that its modified descendants subsequently acquire.[12]

Another crucial point in this theory is the adaptationist programme: if the engine of evolution is natural selection then every particular phenotype characteristic must have an adaptive value because it is the result of selection (one may observe how this concept is present, for example, also in socio-genomics: social forms of behaviour must also have an adaptive value and thus depend upon selected gene characteristics). This aspect of the theory has in the past provoked furious polemics specifically because of the 'political' – and thus ethical-anthropological – consequences of this position.[13] The basic biological problem is whether each form of a living organism is possible but only that form is manifested which adapts to the specific natural environment in which the organism lives. This assertion, which forms the basis of the adaptationist programme, has turned out to be false because there are biological constraints of a very precise character in the morphogenesis and physiology, which principally depend on how embryogenesis proceeds, and the laws of thermodynamics.

If one wanted to be rigorous one would say that at the present moment we cannot find a satisfactory theory of evolution, not least because we are living at a time of a major revolution in both genetic and non-genetic biological knowledge. We are not, therefore, able to consolidate the mass of information that is arriving every day and thus begin a work of synthesis.

It seems to me, however, that it is not ill-advised to ask ourselves if we will ever possess a satisfactory theory of evolution if within this phrase is concealed a mechanistic statement as to the origin of reality. In this sense, the difficulties that are encountered at a scientific level as regards an absolute evolutionism should make people more open to the creationist thesis understood in the specific sense of its ability to provide space to a healthy evolutionism.[14] This thesis – which for Christians has a universal value given that it constitutes a substantial part of the normative contents of their creed – provides a grounding in a plausible way not only for 'evolutionary leaps' but also demonstrates the non-falsifiability of the belief that reality conceals within it an intelligent design and, whatever the case, it also asserts the non-verifiability of the contrary assertion that reason has its origin in pure chance. As the heated debate now underway above all in the United States of America well testifies, pastoral care in this sphere is strongly relevant.

c. *Stem Cells*

Here we encounter a basic biological subject that has been studied for decades by cytologists and by embryologists but only in part by geneticists. Recently this area has received an impulse from post-genomics which made available molecular markers that are able to identify the destiny of a cell at the level of differentiation (the totopotent, multipotent and unipotent stem cells at the outset are identical with each other in morphological terms even though they have already been canalised). In addition, post-genomics allows relevant genes and gene products to be identified in determining what the various pathways are at the level of differentiation.

The most advanced research in this field is that carried out on plant stem cells. Overall, the experiments

on plants have demonstrated the plasticity of the differentiated cells (gametes or somatic cells): they can redirect themselves in their programme of development, going back to being totipotent cells that are able to regenerate adult individuals (that is to say it is biologically possible to effect the cloning of higher individuals) and promote the multiplication of organs. There should not be any biological reason for asserting that all of this is not possible in the case of mammals as well: it is a matter of learning how to do this (with plants thousands of experiments with millions of cells have been required).

Experience with plant cells has, however, also brought out certain serious problems. In all the cases of regeneration through cloning in plants (millions of cases in this field but in the field of animals few cases are available) there is a high frequency of abnormal clones. In addition, scientists are not as yet able to understand what controls to the full the differentiation of cells – some principal genes or interactions between genes or between cells (for example it is certain that the position of a cell in relation to those adjacent to it is important).

In extreme synthesis: even if we know what cells, at any stage of their existence, do not lose their totipotent capacities and even if methods have been developed that allow (albeit only in some species) to make that capacity express itself once again, we do not as yet know what allows and governs the totipotent, unipotent or multipotent capacities of cells, even though it is reasonable to suppose that this question will be clarified at a detailed level because excellent experimental models already exist. A very large number of experiments will be needed to arrive at this goal.

Thus, the question is the following: why should we begin to carry out these experiments on man and not, for example, on animal models? The ethical-anthropological question emerges with clarity. One has the impression that the reason for this choice lies in the fact that experiments on man cost less and are better funded. In addition, they provide the surplus embryos that are frozen because of the absence, in the past, of rules to govern the 'production' of embryos, with a covering of nobility of being a sacrifice 'for science'. (And this obviously reduces the maintenance costs for those centres that have been engaging in FIVET for a notable number of years).

Faced with the possibility that sooner of later it will also be possible for the human species to clone individuals and multiply organs in an effective way (even *in vitro*, as already takes place in relation to certain human tissue – skin, cartilage), we should in a decisive way foster the hypothesis that rather than creating cells and transplanting them into an organism it would perhaps be more reasonable to reactivate and re-utilise stem sections present in each individual (through methods that are beginning to be applied to clinical protocols as well, for example for certain brain sections following ischemic damage).

Above all else, however, it is absolutely necessary to address in an interdisciplinary way the question of a precise definition of what an embryo is and of how, from conception, it is a human being that possesses a personal dimension. In order to do this one cannot depart from a consideration of its development because – to make the point in rough terms but perhaps effective ones – nobody could deny that I today am Angelo Scola aged sixty-four because I was that individual embryo.

The strenuous defence of life from conception until natural death that the Church, together with so many men of other religions and so many secular people, never ceases to advance, expresses her pastoral care towards every individual man and the whole of the human family.

4. Conclusion

From this rapid and ventured incursion carried out by a pastor with the help of a biologist into the field of genetics we can draw a surprising conclusion. Today, it is precisely science and technology that pose the questions that Comte 'prohibited raising' in the name of science.

It is no longer only philosophers, theologians, and scholars of the ethical-social sciences who gather around the inescapable questions that *Gaudium et Spes* formulated with great clarity: 'what is man? What is the meaning of sorrow, of evil, of death, which continues to exist despite so much progress? What purpose have these victories purchased at so high a cost? What can man offer to society, what can he expect from it? What follows this earthly life?' (GS 10). They also irrupt into the laboratories of the men of science, and above all of those scientists who cultivate the knowledge of genetics and biology. Their discoveries are of such an importance and of so radical a character that, and almost without any form of mediation any more, in contemporary society networks impose on the masses themselves the making explicit of the question that the Psalmist directs to God with such intense *pietas*: 'what is man that thou dost regard him?' (Ps 143:3). Indeed, questions about the identity and nature of the *humanum* which, in abandoning academic lecture halls, are proposed by the pages of daily newspapers and by television talk-shows, thereby reaching the people in a capillary fashion, are not few in number. In order to describe the reasons for the unprecedented radical character of this state of affairs which is specific to post-modernity, the French philosopher Rémi Brague asserts that the twenty-first century will be a century of severe contestation between being and nothing. He expresses this alternative in crude terms: 'the central problem is nothing else than the existence of man on the earth'.[15] The tandem 'sciences-technologies' (above all in the fields of biology and genetics), accompanied by the ecological precariousness in which we have allowed the planet to fall and also by the radicalising of a situation of endemic acute poverty in the South of the world, and in particular in sub-Saharan Africa, enables very great masses of men to see that on the threshold of the twenty-first century there is at stake a question of life and death as regards the very existence of every animated species. This is so in a literal sense and this is not a question of words. The clash, if we really see things as they are, is not between civilisations, and even less between religions, nor is it between those who are different (at the level of races, peoples, or cultures). The line of demarcation of a cosmic conflict passes through each man, through

each intermediate body, and extends to civil society in all its local and international dimensions. Each day in each one of us the question strongly irrupts: who guarantees me? In the end who guarantees mankind? The *anxiety* of Hiedegger runs the risk of taking on universal dimensions that will gigantically enlarge the individual dimension. Above all they run the risk if reducing it to a mere first sign of Nothing by tearing them from that function of openness to Being that the philosopher of the Black Forest still assigned to them. This aspect of the laborious travail that characterises post-modern man also requires the risk of Christian witness.

The salvific-sacramental mission of the Church, that is to say pastoral care, is called to intercept the anthropological and ethical basis of these questions by assuring man that the hand of God is at the origin of history and continues to invite him to the responsible exercise of his freedom. In addressing this specific task the Church is helped by the always contemporary appeal of St. Paul: 'test everything; hold fast what is good' (1 Th 5:21). This appeal continues to point out to Christians the road to follow with humble *parresia*.

H. Em. Cardinal ANGELO SCOLA
Patriarch of Venice

Notes

[1] I would like to thank Prof. Carlo Soave of the Department of Biology of the University of Milan for having provided me with valuable bibliographical references and important information.

[2] Cf. *www.soleva.com* e *www.454.com.*

[3] F. VON KUTSCHERA, *Fondamenti dell'etica* (Franco Angeli, Milan, 1991), p. 327.

[4] Cf. L. CAVALLI-SFORZA, 'The Human Genome Diversity Project: Past, Present and Future', *Nature Reviews Genetics* (2005) n. 6, 333-340.

[5] Similarly one may cite the proteomic, but at the level of proteins and not of the first gene products, the inter-atomic at the level of interactions, and the metabolomic at the level of the various chemical components of a cell or an organism.

[6] Cf. 'The International HapMap Project', *Nature* (2003) n. 426, 789-794.

[7] Cf. P. KIBERSTIS AND L. ROBERTS, 'It's not Just the Gene', in *Science* (2002) n. 296, 685ss.

[8] Cf. E.O. WILSON, *Sociobiology: the New Synthesis* (Harvard University Press, Cambridge, 1976); R. DAWKINS, *The Selfish Gene* (Oxford University Press, Oxford, 1975).

[9] Cf. G.E. ROBINSON, C.M. GROZINGER, AND C.W. WHITFIELD, 'Sociogenomics: Social Life in Molecular Terms', in *Nature Reviews Genetics* (2005) n. 6, 257-270.

[10] Cf. M. BUCAN AND T. ABEL, 'The Mouse: Genetics Meets Behaviour', in *Nature Reviews Genetics* (2002) n. 3, 114-123; M.J. FITZPATRICK,Y. BEN-SHAHAR, H. SMID, LEM. VET, G.E. ROBINSON, M.B. SOKOLOWSKI, 'Candidate Genes for Behavioural Ecology', *Trends Ecol. Evol.* (2005) n. 20, 96-104.

[11] The reference is to the 'Princeton Meeting' of 1946 which was attended by such authors as Huxley, Dobzhansky, Mayre and Simpson.

[12] Cf. C. DARWIN, *On the Origin of Species, or the Preservation of the Favoured Races in the Struggle for Life*, 1985.

[13] Cf. S.J. GOULD AND R.C. LEWONTIN, 'The Spandrels of San Marco and the Panglossian Paradigm: a Critique of the Adaptationist Program', *Proc. R. Soc. London B. Biol. Sci.* (1979) n. 205, 581-598; M. PIGLIUCCI AND J. KAPLAN, 'The fall and Rise of Dr. Pangloss: Adaptationism and the Spandrels Paper 20 years Later', in *Trend Ecol. Evol.* (2000) n. 15, 66-70.

[14] 'Evolution, in fact, presupposes the creation, the creation exists in the light of evolution as an event that extends in time – as a '*creatio continua*' – in which God becomes visible to the eyes of the believer as Creator of Heaven and earth'

JOHN PAUL II, 'Address to those Taking Part in the International Symposium on 'Christian Faith and the Theory of Evolution'', 26 April 1985.

[15] R. BRAGUE, 'D'un transcendental à l'autre, IV Forum del Progetto Culturale, Rome, 3 December 2004.

Saturday
19
November

MARIA LUISA DI PIETRO

3. Medical Genetics and Ethics Committees in Hospitals

1. Without doubt, the second half of the twentieth century was a period of great scientific and technological advance: science and technology allowed us to know the structure, the functions and the evolutionary dynamics of living beings, thereby opening up new ways by which to improve the life conditions of man. 'Science and technology': because technology must take advantage of certain knowledge, of a 'science' of how nature works, in order to imitate nature, reproduce it, and correct it, at the same time producing instruments to observe, measure or reproduce things in an artificial; and science cannot do without its operational arm – technology.

A splendid testimony to the capacity, the tenacity and the intelligence of man, science and technology can, however, go against man and create disappointment and anxiety. They can do this to the point that man becomes afraid that he will lose control over the reality that surrounds him. These are the results and the symptoms of a hypertrophy of a feeling of omnipotence. As Bausola writes: 'the modern and contemporary age witnessed, first, the emergence of Promethean man: that man, that is to say, who no longer accepts that he has been made because he does not want to depend upon, or to be grateful to, anyone at all. He is, one can see, an extreme version of the *homo faber* envisaged by Francio Bacon. He is, in addition, today, that man who, through molecular biology and genetic engineering, is planning to modify his own nature'. This process of self-planning, Bausola continues, 'has now reached the turning point, a crisis. This has led to Promethean pride, to Promethean shame…this is the shame that is felt when we are faced with the humiliating level of the quality of the objects that we ourselves produce'.

From pride to shame, and also passing through a fear of its consequences, genetics is, without doubt, the area of research that most brings out the ambivalence of man's relationship with science and technology. And given the inevitable awareness that because experimental science alone can neither perceive nor know the qualitative aspects of reality and the profound value of nature, it is necessary to engage in an ethical reflection on the potentialities of human intervention. As Jonas writes: 'that in general ethics has something to say in relation to questions connected with technology, or that technology is subject to ethical considerations, derives from the simple fact that technology is the exercise of human power, that is to say that it is a form of acting, and all human acting is exposed to a moral examination'.

This is an ethical reflection that finds specifically in genetics the impetus to become 'bioethics', that is to say, according to Pessina, 'critical awareness of the technological society… The term 'critical awareness' indicates the level of moral clarification and assessment of the specific practical and theoretical contents introduced by the technosciences… bioethics may be defined as philosophical activity'.

The discovery of the double helix of DNA in 1953 by Watson and Crick and the discovery of the restriction enzymes, in fact, opened up the way to a total 'manipulation' of man. And as early as 1968 – the term 'bioethics' appeared for the first time in 1970 in the publications of Potter – a public body began to deal with genetic research: during the course of a Senate hearing in the United States of America, Dr. Kornberg called the attention of the members of Congress to the rapid advances in molecular biology and emphasised the impact at a social level that these would have in the immediate future. A few years later, in 1971, Watson himself illustrated to political leaders that the knowledge that had been acquired was by now of such a character that it allowed the manipulation of all the biological processes of life. He was referring, in particular, to restriction enzymes, which would have permitted a successful conclusion to the attempt to integrate the genome of the SV40 virus (which is responsible for tumours in monkeys but not in man, even though an association with brain tumours in man had been demonstrated). Everything was ready for the experiment but at the last moment people's awareness of the risks became very strong – what would have happened if the *Escherichia coli*, a habitual guest of the human intestine, modified in this way, had gone out of control? And if it what would happen if it were to infect the researchers? Might cancer 'epidemics' have been unleashed?

The experiment was not carried out and the response to these concerns was to establish the Gordon Conference (Asilomar I) in 1973. At this conference during Singer and Soll drew up a letter (which was later published in *Science*) in which they expressed to the National Academy of Sciences (NAS) and to the Institute of Medicine the worries of Congress about the risks involved to public health. In this letter they thus called for the issuing of specific guidelines. The NAS created the first ethics committee (chaired by Berg) which drew up a number of recommendations, amongst which was the call to researchers to engage in self-regulation and to suspend voluntarily all those experiments involving genetic engineering which could not be controlled adequately (for example the spread of bacteria that were resistant to antibioetics, the production of dangerous toxins, the spread of oncogenes in bacteria populations, etc.). The Berg Com-

mission also suggested to the National Institutes of Health the creation of a permanent ethics committee to draw up guidelines on the use of recombinant DNA as well as the organisation of an international conference to discuss the risks that were involved. Such were the origins of the Conference of Asilomar (Asilomar II) of 1975 at which experiments at risk requiring the imposition of an international moratorium were identified.

In 1978 the Congress of the United States of America authorised the creation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. This commission examined the emerging problems of genetic engineering, as well as the point of view of religions, educational aspects as regards the general public, the social obligations involved, and the medical-legal, economic and commercial implications. In its report *Splicing Life* (1982), this commission declared that the fears about genetic engineering were exaggerated and observed that the new knowledge of this field should be encouraged because it was a reason for enrichment and for interaction with new and major responsibilities.

Over the subsequent years the questions and problems connected with genetic research grew greater with development of the international programme for the sequencing of the human genome, a programme that permitted the uncovering of the genetic code with all the enormous ethical and social implications at an ethical and social level that such knowledge was to bring with it. In its Universal Declaration on the Human Genome and Human Rights, UNESCO declared on 11 November 1997 that the human genome is a symbolic heritage of humanity which underlies the fundamental unity of all the members of the human family and is a recognition of their intrinsic dignity and diversity. From this preliminary statement derived all the ethical indications on the prohibition of discrimination of the basis of the genetic characteristics of individuals, the legal defence of the person in the case of research into, treatment and diagnosis of his or her genome, the right to be informed or otherwise on the results of research and its consequences, the confidentiality of identifiable genetic data kept or organised for the purposes of research or other purposes, and the prohibition of the cloning for reproductive purpose of human beings. In relation to the carrying out of research this Declaration referred to the responsibility of researchers in the carrying out of research and the presentation and use of the results, as well as to the responsibility of those with decision-making powers as regards scientific policies, in both the public and private spheres. Lastly, reference was made to the responsibilities of states and to the need for solidarity and co-operation at an international level in order to permit freedom of research, the use of results for peaceful purposes, the prevention of forms of abuse, and the international dissemination of scientific knowledge about the genome amongst developing countries.

From what has been said hitherto in this paper, it will be clear that genetic research has become and increasingly privileged subject of bioethical reflection, above all in the domain of ethics committees created *ad hoc* and national and institutional ethics committees, as has subsequently been born witness to by the multiplicity of initiatives, guidelines, recommendations and so forth that have followed one another.

2. Before analysing some of the subjects considered by ethics committees, it may be useful to engage in a clarification. The functions of an ethics committee are essentially three in number. Firstly, it has a *consultative function*, which leads the ethics committee involved to express opinions in relation to specific requests concerning specific questions or to emanate directives, of a non-binding nature from a juridical point of view but certainly with a strong deontological and moral force; secondly, it has the *function of revising protocols on experimentation* applied to different fields of research on man, on animals or on micro-organisms. In this second case the ethical assessment strictly follows reflection on the scientific implications that are present in that particular protocol; and thirdly, it has an *educational function in relation* to health-care personnel. Whereas an *ad hoc* ethics committee or a national ethics committee have almost exclusively a consultative function, an institutional ethics committee can have a consultative function, a function involving the analysis of protocols applied to experimentation, and an educational function as well.

For a long time, with respect to institutional ethics committees, a debate was conducted as to whether the consultative function and the function of analysing protocols for experimentation should be carried out by the same ethics committee or by two separate ethics committees, each one with a specific function. But leaving aside this still unresolved diatribe, it remains a fact that in the field of genetics the questions directed to institutional ethics committees can bear on both the consultative function and the function of analysing of protocols. In the sphere of consultation the questions involved can concern both the ethical aspects of diagnosis and of genetic screening after birth, or prenatal genetic diagnosis with the consequences that this can have on the decisions of the women or the couple involved to continue or otherwise with the pregnancy. With respect to the domain of protocols on experimentations, the questions are concerned first and foremost with the localisation and the identification of genes with the consequences that this can have in the sphere of diagnosis or pharmacogenetics and gene therapy.

Both kinds of questions should be the subject of reflection here: I will dwell upon and analyse only that kind of question that is concerned with research, and in particular concerned with the localisation and identification of genes, given that, amongst other things, the sequencing of the human genome has

opened up new horizons of inquiry and the need is perceived to render valid such knowledge about man by employing research protocols which have well defined pre-clinical and clinical targets.

Given that the ethical value of research as well is always connected with its scientific value and as a result the reason for the experimentation also ends up by being an assumption at the level of an ethical assessment that refers to the value of the research and requires research of a certain value, in the case of genetic research new questions are raised as compared with other types of experimentation. For example, genetic research could lead to discrimination and stigmatisation (so-called 'geneticisation') in relation to individuals and populations and be used to promote a new form of racism; access to the discoveries involved could be limited because of interests of an economic character; genetic research runs the risk of reducing all human beings to their sequences of DNA; and genetic analyses could lead to a lack of respect for values, traditions, and the integrity of populations, families and individuals.

The issues raised also refer to the identification of the subjects of the research that has been carried out, the assessment of risks compared to the benefits that could be obtained, the communication of information, and the re-use of data and samples – these are issues that seem to be a part of the more general subject of clinical experimentation but which in reality have different features.

3. Who is the subject of genetic research? Should families be considered subjects of research or are they only entities with connections with the subject of the examination? Under what heading should the family be involved as regards the subject who is the object of the test? With reference to consent, is the subject of research only the individual from whom a sample is removed or also those who could be interested in the results of the examination? To what extent can one use the clinical data of the subject who takes part in the research when these also concern other people who have not been informed about the research itself? For that matter it is a fact that involvement of the nuclear and wider family often takes place in genetic research – as a result one should act not only in a way that respects the rights of the directly involved subject but also the interests of those who are involved in a wider sense in the research. For this reason, there are those who have suggested that information should be widened when it comes to consent – in addition to that of the individual directly involved – to those who do not take part directly in the research but who could be identified on the basis of the results of that research because they belong to the same family or to the same ethnic group.

A paradigmatic case occurred at the Virginia Commonwealth University in the United States of America in relation to which a national organisation responsible for the safety of people who take part in experiments (Office for Protection from Research – OPRR) took an official stance. This was a study carried out on adult twins in research project carried out to discover the state of health of their parents and other family relatives. The father of a young twin (a woman) who was taking part in the research read by chance the questionnaire that had been sent by post which asked the respondents to indicate pathologies that their family relatives suffered from (such as depression, genital anomalies etc.). The father was worried about the threat to privacy that such information represented. Thus he reported the fact to the OPRR and this report was followed by a statement by the ethics committee that had approved the research protocol and by the suspension of the study by the Food and Drug Administration (FDA). The motivation given was the lack of a request for consent being given to the family relatives involved in this genetic investigation. From this event the conclusion was arrived at that family members must be seen as subjects of research to the full and thus they must be given every guarantee and information, and must also give their consent.

Remaining in the area of family relatives, the question also arises of their recruitment – should it be at the same time as, or after, the recruitment of the subject involved? It is argued that their involvement must as be wide as possible but this raises other questions. For example, to what point must medical privacy as regards the subject be protected in relation to other family members who could ask for personal information about that individual? To what extent could the pressures of the subject involved be so great as to influence the participation of the other family members and vice versa?

In some cases this is a cultural matter or one of being in varying degrees aware that scientific progress can be achieved only at the cost of certain sacrifices. In order to protect the voluntary character of participation it is necessary to understand when this must be requested by a researcher or when, in different fashion, by other members of the family. The risks that arise from an enlargement of the study are added to the other risks of genetic research – risks that are not so much physical as psycho-social and economic in character. Are these acceptable risks? And to what point can they be run?

Genetic studies, indeed, could supply information that could provoke anxiety and confusion in the subjects of those studies, difficulties in family relationships, and significant consequences as regards contracts involving insurance and employment. Hence the need for especial care by ethics committees in being certain that the research protocols do not see the psycho-social risks and the risks of economic discrimination as involving minimal damage.

The broadening of the number of subjects involved can lead to the in-

volvement in genetic research of minors, when, obviously enough, that is to say, the patients themselves are not minors. And thus, in the assessment of the risk-benefit ratio, one must perceive the vulnerability of a minor, above all when the study involved does not involve an immediate benefit for that minor. Reference is made to the fact that in some cases an examination of a minor is carried out solely to reassure a parent or another adult who does not want to subject himself or herself to such an examination. Whatever the case, the inclusion of the minor must be effected, not only in a context of proven benefits but also only after the inclusion of the adults involved has taken place, in a way similar to procedures in pharmacological trials where one proceeds to stages II and III on minors only after the adults involved have already gone through these stages. Thus the judgement of the researcher must be calibrated to defend the minor and, whatever the case, such a defence must be the primary concern of the ethics committee as well.

4. Differently from other medical spheres, genetics has undergone a notable expansion at the level of knowledge but not this is not true at the level of therapeutic supply. At times one is dealing with dramatic kinds of knowledge, or knowledge that is not available or clear, or one can only make calculations in terms of probabilities which are for the most part incomprehensible and can lead to anxiety being experienced by individuals and by groups, something that also generates pressures that are difficult to control. Should these data be communicated to the patient and, if so, when and how?

The positions adopted in relation to these questions and issues are not all of one voice: next to those who propose that the preliminary data should not be revealed there are those who argue that they should be communicated because this could, in some cases, allow action which is, at the least, preventive. But when faced with a decision to proceed with such communication as well, one should assess whether the subject wants, or does not want, to know. For that matter, it is well known that after the emergence of genetic studies the debate was once again opened up on the so-called 'right to know' and 'the right not to know'.

From the point of view of information and communication, the situation becomes even more complex when there is a desire to use elements that were collected previously – does the subject have the right or does he or she not have the right to request that the data derived from the sample that he or she gave previously be eliminated from the research itself? Whereas the right of every subject to withdraw from research that involves further personal involvement is evident, the existence of a right to ask for the data that has been gathered not to be used is less clear. Here, for this reason, a distinction is made between the different situations that may arise. If the use of the data is consistent with the research to which the subject had given his or her consent, it is clear that the request not to use his or her data could alter the research itself, thereby rendering useless the participation of other subjects and the resources that were used up to that point – one can, therefore, say that in this case such a request is not legitimate. If the research that is to be carried out on the conserved samples is different from that to which consent has been given, the person conducting the experiment must acquire the consent of the subject once again and it is legitimate for that person to ask for his or her sample not to be used or to donate that sample after its source has been rendered completely anonymous. However, the new research with the anonymous sample must be approved by the ethics committee. If before beginning the new research on the conserved samples it is not possible to trace the subject to whom the sample belongs and to ask for his or her consent, one can proceed with the research after the source of the sample has been made anonymous, unless, that is, this application of anonymity does not go against the interests of the donor (who may be traced subsequently) or against public interests. In this case, as well, it is necessary to proceed only after approval has been received from the ethics committee.

5. The large number of ethical questions and issues raised by genetic research have also been translated into indications for hospital ethics committees. In assessing a protocol for genetic research such committees cannot depart from assessing certain specific requirements, in addition to those that are shared with other kinds of clinical experiments. In the light of what has been said in this paper hitherto, one may summarise these requirements as follows: that the information on the nature of the research, of the risks-benefits ratio, and the alternatives, should take place within a process of counselling which must precede the whole of the research and continue throughout it; that the information should be clear and comprehensible and take into account not only the subject but also those family relatives who may be involved; that the consent should be free of forms of coercion of a scientific or medical character or exercised by other authorities; that the choices of the subject (or subjects) should be respected as regards the conservation or other uses of the biological material that has been removed from him or her; that the choice of the subject (or subjects) to be informed or otherwise on the results of the research or on possible or accidental discoveries must be respected; that full confidentiality as regards the genetic information that has been acquired should be maintained and that indications should be drawn up for its codification, and as regards control over access to it and the planning of the conservation and transport of such samples, as well as information derived from them; and that there should constant surveillance and monitoring.

All of this has the aim of defending the subjects of research. But a further form of defence must take place – and this is something for which an ethics committee must make itself responsible at the level of its educational function – through the training of researchers. This is because the guidelines, the deontological codes and informed consent are only points of departure, although they certainly cannot be dispensed with: the best guarantee of safety for the subjects of research is the suitably enlightened ethical conscience of researchers.

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FRANCESCA PASINELLI

4. Genetics and Society

Patients' associations, patients themselves and their families are amongst the most enthusiastic supporters of biomedical research. It is easy to grasp the reasons for this: to discover that one is the carrier of, or affected by, a genetic illness, which in the majority of cases is very serious and renders its sufferer an invalid, means to find oneself facing a painful experience which is often lived out in loneliness and from which one cannot escape, at least given the present state of knowledge in this field. The prospect for the person involved is that of a chronic illness, a progressive disability and, at times, an early death, all of which are experienced in a state of powerlessness. Given that genetic diseases are in general rare when considered individually, the patients affected by them and their families are often isolated, unaware most of the time that there are other people in the same condition as them who are engaged in an exhausting search for places of care and assistance that are dedicated in their approach and specialised in their capabilities: a family doctor can pass the whole of his or her professional life in a very praiseworthy way without ever coming across a genetic illness and he or she is thus unable to offer the help that is expected of him or her in such cases.

The initial motivation of such patients in joining together in organisations that represent them arises from their need to reduce their isolation and to find support at a social level and at the level of assistance. The availability of a cure is thus their most urgent need and the hope of meeting that need is centred round research. It is with this objective that patients' organisations promote the raising of money intended to finance research. The charities that are concerned with biomedical research have become over the years important actors on the international stage of scientific research. They nearly always represent groups that are centred round illnesses and the families of patients who suffer from such diseases.

For the most part their mission is research directed towards finding a cure for, and the improvement and prevention of, the illnesses which form the subject of their attention. The relative importance of their role compared to state investments varies from country to country. In the United States of America, for example, they are responsible for only 2.5% of total investments in biomedical research of an industrial and non-industrial character. In Great Britain, on the other hand, their contribution has acquired an increasing importance, and this to the point of equalling levels of government investment.[1] It is calculated that the financing of work that gives rise to a scientific publication by British scientists is to be attributed to a charity in the case of 33% of the publications from Great Britain to be found in specialist international journals. For this reason as well, British charities by now sit at the tables where major strategies are formulated and are privileged interlocutors with government bodies as regards research in this field.

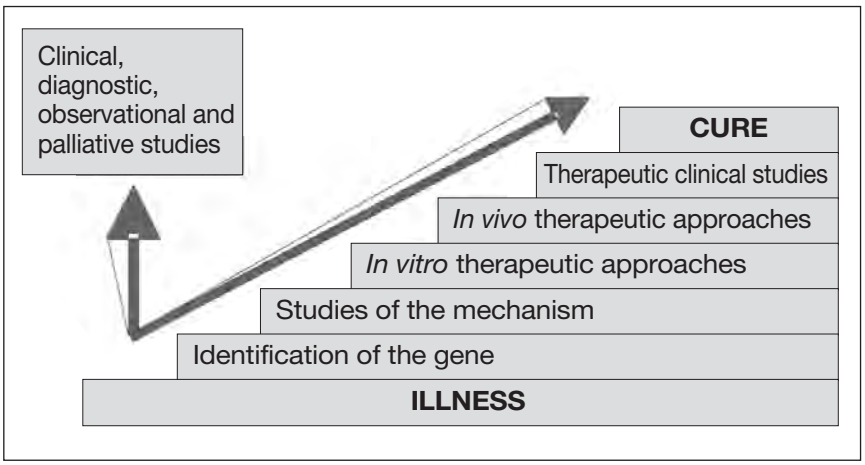
Given that the money that is raised through campaigns directed at a public that is non-differentiated and 'profane' compared to the research that is financed, the ability to society to influence research policies is becoming dominant. From esoteric research, the concern solely of experts that was decided upon in narrow circles, we have moved to research influenced at times in determining fashion by what pleases the general public and thus by the capacity of those who raise funds to be convincing and credible.

For these reasons, the responsibility of those who run these charities is rather great, both in terms of a correct and rigorous allocation of the funds that have been raised and in terms of a precise, documented and never sensationalistic account of the results that have been achieved.

There will now follow an account of the experience of an Italian charity, the Telethon Charity. Created by the Italian Union for the Fight against Muscular Dystrophy (UILDM), Telethon is a non-profit making organisation which raises funds for research to combat neuromuscular diseases and other genetic diseases. Telethon is known principally for its television activities and often it is wrongly believed that Telethon is exclusively a television marathon. Its mission, instead, is move scientific research towards the cure of muscular dystrophy and other genetic diseases, giving priority to those diseases which because of their rarity are neglected by great public and industrial investments, through the financing of excellent projects of research and the best researchers in Italy. From the creation of Telethon at the end of 1990 to today, thanks to the funds that have been raised, 208 million euros have been invested in research, thereby financing 1,450 projects, 2 institutes (Tigem and HSR-Tiget), 27 posts for 'Telethon Scientists', 64 scholarships or grants, and 68 services to help research. The promotion of research by Telethon is principally directed towards universities and research institutes of an academic character.

The ideal pathway to achieving a cure for a genetic illness involves different stages of research. Basic research moves from the identification of the defect – the identification of the gene – to the study of the physiopathology and the mechanisms by which it operates. And to do this it is necessary to create laboratory models that reproduce the illness. This research is still very far from the stage of application at the level of the patient but it is of fundamental importance in the understanding of the malady concerned and the establishment of therapeutic

Fig. 1 - The research ladder



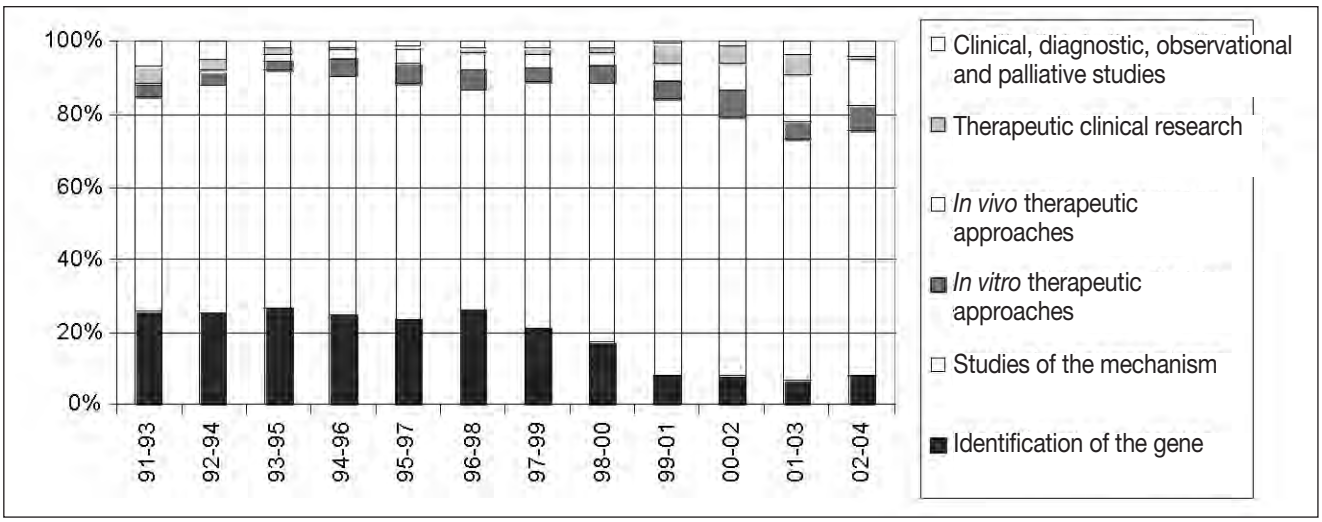
strategies to combat it. The potential therapies are first tested in the laboratory and then on patients in the form of clinical experiments (Fig. 1.).

To provide an overall vision of the projects that have been financed and in order to engage in a management of the funds that goes in the direction indicated by the patients who founded the organisation, the projects financed by Telethon have been labelled so that they can be placed on one of the rungs of the research ladder (Fig. 2). It is interesting to observe that over the years funding has progressively moved from the lower rungs towards those more typical of so-called translational research, that research, that is to say, that is directed towards the creation of application of therapies to patients. To move from 'the laboratory bench to the patient's bed' is the objective pursued by Telethon and these data confirm the soundness of the strategy which, although on the one hand it does not neglect the quality of science, on the other hand acts to favour those projects that move in the direction of therapy.

Like the majority of charities that depend on the funds that they raise, Telethon also operates principally by financing projects through competitive calls. Through this modality funds are provided for the careers of young scientists who do not have a permanent position in Italy and who want to begin their own independent research and also for the research projects of scientists who already work in the non-profit public or private research structures of Italy. Without seeking perfection, indeed with the awareness of the possibility of error, the system adopted for the choice and assessment of the projects to be financed is the only one that is considered reliable at an international level – that of the employment of a peer review. In English this phrase refers to the assessment of projects carried out by experts in the field under review who do not have conflicts of interest with those who present the project. A process of selection by the peer review method is structured in this way not in order to seek the absolute objectivity of the assessment but in order to minimise error. Through a competitive call and by means of a careful assessment the aim is to finance excellent research that will be able to compete in the international research arena.

A transparent account of the employment of funds and the results that have been achieved is one of the points of the mission of Telethon – the Foundation has the obligation to measure and assess constantly the social utility of the activity that is engaged in. Although the principal objective remains the creation of therapies, the assessment of results *in itinere* is linked to a series of indices. The results of a scientific work must be communicated by means of a publication in specialised reviews. The bibliometric reviews are principally based upon counting the number of citations of a scientific article in other scientific publications. This scientific citation, that is to say a reference to a result published previously, is a yardstick of the impact that that result has had on the scientific community. In other terms, the more an article is cited the more it is likely that that article has produced an effect in the scientific

Fig. 2 - Distribution in percentages of the funding for Telethon research projects on the research ladder for the successive three-year periods of 1991-2004. Source: Centro Studi Telethon.



world and constitutes a basis for further research. In order to obtain a correct measurement of the impact of an individual article, therefore, it is necessary to use the citation index, that is to say the number of citations achieved by that work. The calculation of the citation index has to be requested from the Institute for Scientific Information (Thomson ISI, Philadelphia).

In using the citation index as an indicator, the publications generated by the funds allocated by Telethon perform better than the publications generated in the principal fields of biomedicine in Italy, Europe and globally, equalling the level of the United States of America, which, indeed, has the highest standard. This result provides a very important indication, namely that the system for the assessment of the projects to be financed functions as hoped for in selecting those projects that are really excellent and have optimal probabilities of success.

The principal result achieved hitherto, however, has been the gene therapy carried out with success on six children affected by a grave congenital immunodeficiency (ADA-SCID). This was the first intervention in the world upon this malady and at the same time the first protocol of gene therapy in which this very innovative technology was demonstrated to be at one and the same time both effective and safe. This protocol, which was created at the Telethon Institute of Gene Therapy in Milan, was recently indicated by the Food and Drug Administration of the United States of America as the protocol of reference for all those centres that intend to treat this grave genetic illness.

Recently, the Telethon Foundation received from the EMEA, the European regulating body that is responsible, amongst other things, for the registration of orphan pharmaceuticals, recognition of its gene therapy for ADA-SCID as an orphan pharmaceutical. The process to obtain its registration is currently underway. The aim is to move the therapy out of the stage of research and make it accessible to patients within the context of normal, albeit rigorously specialist, medical care and treatment.

The availability of privileged pathways for the registration of orphan pharmaceuticals, like the introduction into industrial development programmes of products such as vectors for gene therapy, or refunding for certain treatments of a very expensive kind as well by governments, undoubtedly constitute a success that has been achieved by parents' associations.

In all of this the involvement of public opinion has been, and is, of determining importance. For this reason as well, charities that finance research for patients should operate through a rigorous management of their expenditure and through a peer review process that allows the pursuit of scientific excellence: the public with its generous donations and patients themselves must be reassured through an accurate monitoring of the activities involved and their constant direction towards strategic objectives of which they become aware.

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Note

[1] *USA:* Moses *et al., JAMA,* 294: 11 (2005); UK: AMRC websit (*www.amrc.org.uk*).

XAVIER POMES

5. Economics and Genetics

I would like first of all to greet you on behalf of the Order of St. John of God as I myself would also like to greet you, and to thank you for wanting our participation in this twentieth international conference, which in our view addresses one of the most complex and beautiful challenges raised at the present time for society. At the same time, I believe that it is right that we should congratulate the Holy See for its courage in being involved in a subject that concerns very modern technology so as to offer open space to a multi-disciplinary debate, and above all for having involved us in, represented and directed an ethical-moral debate on a subject that is generating discussion in a number of forums.

In recent days we have listened to scientists who from their areas of study have illustrated to us the complexity of the genetic system and its pathological manifestations, and to theologians, ethicists and men of the Church and of other religions who have illuminated us on the moral, ethical and pastoral implications of the knowledge and use of the information contained in genes. Today, there will be a discussion of the aspects that are usually forgotten by the scientific community: those, that is to say, connected with the real repercussions of such knowledge for the real population or those which, in terms of public health, we may call 'the move from efficacy to effectiveness'. In this society, in which it is almost impossible to keep abreast of matters because of the extreme speed of events, it is advisable to remember that the introduction of this new technology into habitual health care practice has both good and bad consequences, beyond that which is rigorously clinical or scientific, that which is a matter of health care.

The transformations that genetics will induce in the legal, social and educational fields will come from the economic repercussions that the emergence of this new industry is able to generate. When we refer to the economic repercussions we must bear in mind both the positive and negative impact, but without forgetting what the policies are that we should propose on the basis of these predictions so that the negative impact will be minimal and the positive impact maximal. I will then attempt to dwell upon the following major subjects: the sources of costs and possible policies in the economic sphere.

The introduction of any new technology into the economic field habitually generates contrasting feelings: on the one hand there are the business men who see the possibilities that arise for business and the market, and on the other there are governments which initially see only the high cost that this generates.

My impression is that if the biotechnological market, according to what genetics and genetic engineering emphasise, organises itself adequately, the balance between costs and earnings must be positive not only in economic terms but also in social terms. And I believe that the principal sources of costs will be determined by the increase in the cost of the process of diagnosis, by the increase in the prevalence of illness, and lastly by the increase in the cost of treatment as well.

The *increase in the cost of diagnosis* seems to be a clear and linear phenomenon because a diagnostic technique is being added to the arsenal of such techniques that presently exists. It would be reasonable to think that this diagnostic technique will replace those that already exist because it is more sensitive, that is to say because it allows a higher level of certainty about the presence or absence of an illness following the result of a test.

However, neither the logic of health care nor, probably, the studies of efficiency, will confirm this. From an exclusively economic point of view, and given that the cost of genetic techniques remains so high, it would be an optimal approach to adopt strategies that increase the process of diagnosis by initially employing those techniques which, although they are not those that are most in view (in colloquial terms those that we could describe as being more reliable), are, however, those that are most efficient (greater return for a lower cost). We may think here of a patient afflicted by colon cancer: the use of computerised tomography has not replaced the systematic use of simple radiology, in the same way as if a genetic probe existed this would not take the place of tomography.

Equally, if a genetic test could determine the presence or absence of an illness this would not eliminate the need for those other tests that allow an analysis of the morphology, extent or gravity of the illness. To continue with the example of colon cancer: the presence of genetic material that can be identified as coming from cancer cells would not eliminate the need for an angiographic morphological study…

The second source of costs is *the increase in prevalence*. The introduction of those technologies that are most sensitive as regards the diagnosis of certain pathologies has always raised the prevalence of situations involving study and this also seems to be a logical effect: since the test is more sensitive one can carry out a diagnosis of more people without symptoms or with symptoms that are not very clear. It also seems to be logical to think that an increase in the level of prevalence of such tests will not be free because this new part of the population will request health care, in the form of medical examinations, diagnostic controls, forms of treatment…The mere observation of

these facts can cause confusion in our minds as regards the increase in expenditure in the long term: if we have a test that allows conventional techniques to advance in the diagnosis this also means that we can act earlier at the level of prevention even when the individual does not have symptoms or these are incipient.

Thirdly, let us suppose that the introduction of genetic tests in health care practice *increases the cost of treatment*. As is the case with diagnostic methods, we could refer to an increase in the cost of a 'product' because of the increase in its complexity. This also seems logical. However, we should also consider treatment as something that goes beyond medical action, which is circumscribed in time to various extents. If we consider an illness in all its range, from its appearance to its cure or to the death of the individual concerned, we can see that what we traditionally see as medical action only involves a small fraction of the total cost of illness, to which we should add the cost of rehabilitation, the cost of being absent from work, the moral cost (if it is actually the case that this is quantifiable in ways that do not involve doubt), the cost for the person's family and for society as a whole, the cost of disability… If we see illness as a broad-ranging process and not as an isolated event, it is easier to understand that the cost of a procedure at a given moment is insignificant compared to the resources that are saved through the prevention of the appearance of future complications.

I would like to illustrate a very relevant case – pharmacogenetics. We know that the metabolism (the pharmacocynetics) of certain pharmaceuticals is not the same in all individuals and that this in part is due to the composition of the hepatic cytochrome P450, which is determined genetically. This variability in pharmacocynetics gives rise to an important variability in the reaction to doses and contemporaneously places the health of many patients at risk who, because they are 'slow metabolisers', receive standard doses of pharmaceuticals but are thereby treated with doses that for them are potentially toxic. Thus genomic knowledge allows us to adapt doses to the individual thereby ensuring that the treatment is more efficient and safer, reducing, as a result, the probability of future complications because of the use of erroneous forms of therapy.

Thus I believe that the message that should be transmitted as regards the increase in costs brought about by the appearance of technology is clear: although it is certain that to begin with costs can increase, in the medium and long term I believe that genetic engineering will open up an important range of possibilities, on the condition that we know how and when to utilise them in a rational and efficient way. The problem, as always, is not whether it costs more but how much more we will obtain by paying a little more. In the case of genetic techniques the increased cost is known or calculable and what we have to clearly establish is the efficacy of these tests and their ability to modify in a noticeable way the development of an illness. To know that a person is predisposed to suffer from a malady brings only anxiety if we can do nothing to modify the development of that malady.

However, we should not be content with this message, which is relatively optimistic, alone, given that the efficiency of the technologies in

question do not solve another problem, which is perhaps the principal problem: that of access to these tests and their widespread use. From our point of view, the greatest risk raised by genetics at an economic level (and thus at a social level as well) is that of *unfairness at the level of access*, that is to say that in many situations the less well-off do not have access to these technologies, or expressed in rougher terms that those most in need continue to be unable to benefit from the potentialities of this industry.

And we cannot forget that hitherto a not negligible part of the research that has allowed the development of this industry has been financed with private capital and promoted with a commercial approach because patents have been sought and obtained on the various products that are derived from research. The absurdity appears even greater if we bear in kind that sequences of DNA have been patented without any apparent purpose, as genes without any known function have been, as though one day the function of such genes will be known about.

Patents, conceived as a method by which to assure a return on the investment of a businessmen and as a method by which to stimulate research and development in relation to new products, should be associated in this case with certain prices that constitute an abuse and an example of monopoly power. In line with the logic of business, these prices are above the optimal price, which, in addition, are in fact established by taking as a point of reference the income levels of the developed countries, as a result of which most of the populations of all countries with medium or low incomes are excluded.

The answer from the point of view of the regulation of the market is simple. First of all, it would appear to be sensible not to concede rights of property (that is to say patents) to those genetic sequences that do not have a known function. The risk, in addition to going against every moral instinct, is that of falling into what some people, to paraphrase Garret Hardin,[1] have termed the 'tragedy of anti-commons', in which the proliferation of property rights over parts gives rise to powerful disincentives as regards the use of those parts overall. That is to say that if in order to develop a technology I have to subtract the higher costs of an infinity of small patents it is probable that I will never seek to develop that technology.

A second element which can reduce the impact of patents is the involvement of governments in research projects. The clearest example of this was the joining of the efforts of private industry and the European and North American governments in the Human Genome Project. Just as costs were then re-

duced by involving both public and private researchers, so one should now facilitate the ability of public research centres (in essential terms university centres) to create unions with private industry so that the results of research can be commercialised not at a monopolistic price but at a market price.

Other alternatives in the fight against monopolies would disappear because governments in a united way would buy patent rights so as to be able to use the product, or at least part of the presumed benefit for the private investor, because the price would be nearer to the optimal price on the market. Answers such as those proposed by some governments which authorise their Ministers of Health to force companies to sell their rights at 'reasonable prices' do not seem to be very sensible from a business point of view and at the level of necessary reciprocal understanding and co-operation.

To combat monopolies, governments must deregulate the market so as to help small investors to enter the market and *contest* the monopoly, or offer fiscal benefits to those small scale companies that invest in the biotechnological field. Equally, they should offer fiscal benefits to those people or companies who invest in research or do not adopt monopolistic positions. Governments, in addition, should facilitate the merger or purchase of small companies to the point of acquiring a sufficient scale so as to be productive, and finance the costs of research and the development of biotechnological material. Equally, one could reduce the bureaucracy that weighs upon authorisation procedures for the developments of industry or facilitate access to these products on the market, thereby reducing the costs for the businessman.

From the point of view of government, as we will see, there exist measures that can be adopted to avoid the unfairness due to the cost of a product but we cannot avoid the initial fear generated by genetic information, namely that of *horizontal unfairness*, where individuals are afraid that they will be stigmatised because they are the carriers of a potential illness.

The regulators, in the same way in which they must avoid prices that go beyond their cost, must prevent the misuse of the information that is contained in each of our cells. There is a real risk of an inadequate use of genetic material, especially in those countries where the public health care system is weak or maintained by a strong insurance sector. The case of the United States of America is very instructive: on two occasions Congress discussed legislation that prohibited discrimination on the basis of the result of genetic tests, but these measures, perhaps because of the major economic interests that were involved, were not approved by the Senate. In Europe the trend has been different, given that it is insurance companies that have adopted internal codes, based on various criteria, to avoid the use of this information

Real fairness is perhaps the most important battle, and this is a battle that is about to be settled. If we do not manage to ensure that access to genetic tests is widespread and not limited we will run the risk of creating once again technology for elites, a new mechanism by which elites perpetuate their positions, not least when we bear in mind that at the present time we only have genetic technology that indicates risks and allows us to predict that the ability of the less well-off classes to pay for it is very low or non-existent.

First of all the Church must not and cannot remain at the margins of this process. Although it is certain that her legislative power is limited this does not exonerate her from her responsibilities and even less from her mission of forging individuals who are morally capable and free! The Church must employ her immense moral strength and ability to mobilise people in order to call for research of an ethical character, that is to say that research should not be used to discriminate but to integrate or to prevent. Equally, the Church must promote debate and bring this technology close to everyone so that in a uniform way an appeal is made to use it and make its employment widespread. This is because the Church is the spokesman of the marginalised and the scourge of those who engage in abuse.

In the same way the Church cannot fail to include Catholic universities in this process. In Catholic universities priority must be given to research into those genetic techniques which will subsequently have greater impact at a social level, that is to say which are more efficient from a social point of view and at an individual level obtain only minimal benefits.

Lastly, in my opinion the Church must also take a stance by condemning the unfairness that the new technologies bring to the fore and mediate in such a way as to develop agreed solutions between business and governments so that such technologies bestow greater benefits on the less socially fortunate. In low or medium income countries, the Church must make herself the promoter of the approach that advocates fairness so that governments allocate a part of their scarce results to those programmes of genetically determined prevention which are shown to be effective, and she should co-operate with governments in implementing agricultural and/or veterinary policies that take into consideration the advances in genetics.

A short time after learning about the structure of the double helix, the fiftieth anniversary of which we have just celebrated, Watson and Crick declared: 'It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material'.

Now that we know that its widespread and efficient use can only bring benefits to everyone, we can say that 'it has not escaped our notice that the development of genetics suggests the possibility of a new fracture between the rich and the poor'. Whether this will take place depends in part on our wishes, on our capacities and on our future actions.

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Note

[1] G. HARDIN, 'The Tragedy of Commons', *Science* (1968): 162; 1243-1248.

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6.The Training and Up-dating of the Pastoral Worker in the Field of Genetics

As a Church in the World

As a *Church in the world*, the pastoral worker exists to evangelise; and pastoral workers in the field of health, in particular, are called upon to actuate the humanitarian and liberating action of the Kingdom of God where the human being is most vulnerable in his dialectic of health-illness, in his experience of pain, and in his vital processes from birth to old age and death. These are the strong events of human existence where people usually pose the ultimate questions about life itself, and which affect and involve everyone.

The Evangelising Guarantee

In his pastoral activity, which was in conformity with the times in which we live and with the questions that we have to address, Pope John Paul II required his pastoral workers to have a process of ongoing training which helped them to be the guarantors of humanitarian and liberating evangelisation in the world of health and illness.

In the Health-Care Field

Through her action of assistance and pastoral care, the Church continues to proclaim today as well the *gospel of life*; in the concrete field of health care the Church 'is particularly aware of the need to broaden all possible knowledge at the service of human life, so that where technology is unable to provide exhaustive answers, "the law of love" may come to light.'[1] However, this requires that all people involved in some way with pastoral care in the health-care world, whether they are health-care professionals, people who provide assistance to sick people, or scientists of life, 'are required to be properly trained in morals and the problems of bioethics, to show clearly that science and technology, at the service of the human person and his fundamental rights, contribute to the overall good of man and to fulfilling the divine plan of salvation.'[2]

In Relation to Vital Questions

In this sense, pastoral workers who feel called to engage in evangelising action in the world are ready to commit themselves to this task with all their good will and with all their faith, although they are aware that nowadays their 'good will' is not sufficient, even though this good will is illuminated by faith. They feel the need for a form of training that is increasingly complete and specific as regards the vital questions that influence people in general and the people with whom they have to carry out their mission in particular. Of urgent importance, as well, is the duty to respond to a need at the level of training whose finality is not only to increase and to share faith but to ensure that our pastoral action near to people is fully effective.

The Question of Genetics; the Field of Reference

With respect to the field of genetics, which is the concern of this paper, we are aware that the sequencing of the human genome has raised major social expectations. The great questions of genetic manipulation at the level of the curing and prevention of illnesses, of research in the field of eugenics and all its possibilities, of the beginning of human life and assisted reproduction, of establishing the value of human existence on the basis of genetic characteristics, amongst many others, have gone beyond the ability of pastoral workers when they develop the evangelisation of the health-care world. Such pastoral workers usually find that they are without answers and do not have the ability to engage in dialogue because of a lack of knowledge in this field of genetics: they thus feel unable to offer help as believers in relation to these questions. And it is these questions, and other questions connected with these, that make up, in precise terms, the field of reference within which pastoral workers must to a very great extent carry out their evangelising action. Hence training is considered of urgent importance so as to position us more adequately in this context by knowing about it better, by clarifying our identity and our mission, and thus by being able to provide help through a coherent form of pastoral care.

The Positive Character of Scientific Progress in Relation to the Human Genome

John Paul II during his pontificate was ahead of our time in telling us that 'scientific progress such as that involving the genome is a credit to human reason, for man is called to be lord of creation, and it honours the Creator, source of all life… All interference in the genome should be done in a way that absolutely respects the specific nature of the human specie, the transcendental vocation of every being and his incomparable dignity. The genome represents the biological identity of each subject;

furthermore it expresses a part of the human condition of the being desired by God for his own sake through the mission entrusted to his parents'.[3]

In line with what John Paul II said, Prof. Angelo Serra observed years ago in relation to genetic engineering that 'genetic engineering is an evident demonstration of the capacity for intelligence that God wanted man to share in. The Catholic Church', he went on, 'has never demonised research that aims at discovering and employing genes (that is to say the coded information that governs all the development and the working of the organism) for good ends such as overcoming illnesses. The 'yes' to genetic engineering has, however, a precise pre-condition: science and technology, once the secrets of nature have been discovered, must use them for the good of man. Catholic thought does not underestimate the advantages and the risks that genetic engineering involves'.[4]

A Culture of Health that is more Human Because of a Training in Genetics

Faithfulness to the gospel of health on the part of pastoral workers includes the promotion of a more *human culture of health*, a culture that respects and effectively recognises the dignity and the rights of all people, a culture that illuminates in a positive way such very important subjects as the *defence of, care for, and the quality* of, human life, above all at a time when new technology is increasing the moral conflicts that exist about the origins, the end, and the intermediate stages of life.

Consequently, it is necessary for pastoral workers to receive training in the field of genetics as well as up-dating on the most basic questions that influence our behaviour in relation to the beginning and the end of human life, genetic manipulation, and research in the field of genetic therapy.

Basic Descriptions of Training

1. The 'up-dating' of pastoral workers in the field of genetics must begin around the concept itself of the 'genome'. They must know that we are referring to the set of genes that specify all the potentially expressible characters of an organism of both the external (xenophenotype) and internal (endophenotype) kind. In the case of the organism of the human species (a eukaryot) there is a proportion of DNA that does not encode for any gene and because of this fact its significance in most cases is unknown. They must know that the genetic message contained in DNA lies in the sequence of its four nitrogen bases (adenine, cytosine, guanine and thymine) and that this sequence determines the sequence of amino acids (20) through the processes of transcription and translation, and thus the functional specificity of the protein that encodes, and gives rise to, each of the genetically unrepeatable individuals.[5]

And together with the elementary knowledge that can be acquired about this part of genetics, known today as genomics, which deals with the molecular dissection of the genome of organisms, the training of pastoral workers in the world of health should also concentrate on the human genome as such: not so much in order to know its sequential character as in order to know about the consequences – the good consequences – that may be generated for mankind. They should also know that the results of the Human Genome Project are opening up the way to genomic medicine and to pharmacogenomics, to the development of clinical genetics and to genetic consultancy.

The importance of training in this field of genetics lies in the repercussions of its results both for diagnosis, prognosis and clinical therapy and for the relationship between the medical doctor and the patient, which is, indeed, the specific domain of pastoral action.

2. Special interest in the field of genetics was stimulated by the Universal Declaration on the Human Genome and Human Rights of UNESCO of 1997, whose great catalyst was its then director, Prof. Federico Mayor Zaragoza, who is present here amongst us today. This Declaration must also be known about by pastoral workers who engage evangelising action, above all as regards the questions relating to the beginning of life and genetic manipulation. In this document attention is paid to the questions connected with human dignity and the human genome, the rules governing the practice of scientific activity, solidarity and international co-operation, and the promotion of the principles that underlie the Declaration itself and its application. These are questions which, although they are drafted in general

terms, imply a universal process of awareness of the need for ethical reflection on science and technology. This is a universal 'process of awareness' that we should share with pastoral workers in the world of health who are called to be a 'church in the world'. The value of this Declaration, on the one hand, to employ the words of Prof. Mayor Zaragoza, lies 'in the balance that it establishes between assuring

respect for rights and fundamental freedoms and the need to guarantee freedom of research'. On the other, the Declaration stimulates us to engage in reflection, in discussion, and in an in-depth analysis of human problems in the field of genetics.

In addition to this important document of UNESCO, the training of pastoral workers must be implemented employing the documents issued by the Consultative Committee on Health Care Research of the World Health Organisation on genomics and world health, and the most recent report of the secretariat of the World Health Organisation (21 April 2005) on the 'Control of Genetic Illnesses'.

An inescapable subject in the training of pastoral workers in health is knowing about and disseminating with faithfulness and precision the thought of the Church on the facts that are taking place and could take place in the field of genetics. Here the 'Address of the Holy Father John Paul II to the Plenary Assembly of the Pontifical Academy for Life' of February 1998 is very illuminating. In this address His Holiness John Paul II declared: 'I feel an obligation here to express my concern over the spread of a cultural climate which is steering prenatal diagnosis in a direction that is no longer one of treatment for the sake of better accepting the life of the unborn, but rather one of discrimination against those who do not prove healthy in prenatal examination. At the current time there is a serious disproportion between diagnostic possibilities, which are progressively expanding, and therapeutic possibilities, which are scarce: this fact raises serious ethical problems for families, who need to be supported in welcoming newborn life, even when it suffers from some defect or malformation. And with even more precision he added: 'it is necessary to denounce the rise and spread of a new selective eugenics, which leads to the suppression of embryos and foetuses suffering from any disease. Sometimes baseless theories about the anthropological and ethical difference of the various developmental stages of prenatal life are employed: the so-called 'progressive humanization of the foetus'. Sometimes an appeal is made to a mistaken idea of the quality of life, which should – it is said – prevail over the sacrednes of life. In this regard, we cannot fail to ask that the rights proclaimed by the conventions and international declarations on the protection of the human genome and, in general, on the right to life be enjoyed by every human being from the moment of fertilization, without any form of discrimination, whether related to genetic imperfections or physical defects, or to various stages of the human being's development.'

Thus it is of primary importance to know about the papers and deliberations of the fourth plenary assembly of the Pontifical Academy for Life and in particular the contents of its final communiqu which may be seen as a guiding criterion for the activities of pastoral workers in the field of genetics.

In this context of the contributions of the Church to the training of pastoral workers should be included the 'Observations' of the SC (Paris, 11 November 1997) on the 'Universal Declaration on the Human Genome and Human Rights' where emphasis is laid on questions such as informed consent, the use of the results of a genetic test, the conscientious objection of researchers and health-care workers, the rejection of cloning and the fact that embryos and foetuses are not referred to in the UNESCO Declaration.

3. In addition to the objective descriptions that may be added to training in genetics, it is important that pastoral workers adopt a necessary approach – that of recognising the good that scientific progress connected with the human genome brings with it. In relation to interventions on the sequence of the genome, pastoral workers must bear very much in mind that such interventions must be carried out with absolute respect for the specific character of the human species, the vocation to transcendence of every human being and his incomparable dignity.

In addition, for pastoral workers it must be incontestable that the fact that we can know about the genetic map does not allow us to reduce a person to his or her genetic inheritance and the possible alterations that are written into it. A human being as such goes beyond the set of his or her biological characteristics. And there is a fundamental unity in which the biological aspect cannot be separated from the spiritual, family and social dimension without the grave risk arising of eliminating what constitutes the very nature of the person and converting him or her into a mere object for analysis. It is the human person, precisely because of his or her nature and singularity, that is the norm for all scientific research.

As regards the dignity of the human genome, pastoral workers should have a clear idea of its foundation. Article 1 of the Declaration on the Human Genome and Human Rights of UNESCO says that 'the human genome underlies the fundamental unity of all the members of the human family and the recognition of its intrinsic dignity and diversity' and this could be taken as meaning that the foundation of the dignity of a human being is the genome as such, where in reality the contrary is true: it is precisely the dignity of a human being which confers value on the human genome, and thus the human genome must be protected. The dignity that bestows value on the genome has its foundation in what distinguishes a human being from other living organisms: a human being is a subject endowed with freedom, a subject with reason and the capacity for dialogue, a subject able to think, to feel and to choose. For this reason, a human being must be considered as an end in himself or herself and never as a means. In this sense, it is our faith that allows to discover the foundation of the dignity of human beings and thus the foundation of the dignity of the human genome in a being who has been created in the image and likeness of God. 'And given that man possesses only his own genome in the same way as he possesses his own body and no other, it is the dignity of the human being that confers dignity on the genome'.[6]

4. Another important approach that is required of pastoral workers is that of recognising the meaning

of the responsibility of those people who dedicate themselves to research into and reflection about the new data and facts offered by the advances in genetics and genomics, with a view to achieving the greater wellbeing of people and an improvement in human health. This approach is previously and absolutely required when we consider those people who are involved in these forms of scientific progress if we want to achieve the wellbeing of all human beings. This is because the treatment of material that is strictly human, in connection with the very serious questions of the status of embryo cells and the use of embryo mother cells, absolutely requires that everyone addresses such treatment with the greatest responsibility. Such responsibility obliges us to take the facts, the practical consequences of our actions, and our interpretations into account.

The need to act with responsibility becomes greater in the case of the creation of a new organism or a new human being or in the case of depriving the future of certain specific biological realities such as zygotes, which are destroyed.

As regards the consideration of the human status of the embryo, it is obvious that our society is clearly divided. The arguments used by those people who think that the zygote is not a human reality that is underway bring to bear a logic of argument that is no less forceful that of those who assert that a zygote is in fact a human reality that is underway. For this reason it is advisable for pastoral workers to recognise the nature of the responsibility from which these arguments are generated, above all in the case of defining the constituent period of a human being.

Without abandoning our own arguments, without abandoning our own beliefs and convictions – which are always of great value – we are open to considering other arguments that are supported by facts and by interpretations and are generated by responsibility.

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Notes

[1] JOHN PAUL II, Apostolic Letter, *Motu proprio Vitae Mysterium,* n. 2.
[2] *Ibid.,* n. 3.
[3] Cf. 'Discorso all'Accademia Pontificia delle Scienze*?*, *l'Osservatore Romano* 4.11. 94, p. 20, nn. 3-4.
[4] A. SERRA, *Zenit*, 3.5.2000.
[5] J-R. LACADENA, *Genética y bioética* (Descl? de Brouwer and U.P. Comillas, Madrid, 2002), pp. 275-276.
[6] I. NUÑEZ DE CASTRO, 'Reflexiones éticas ent orno a la declaración universal sobre el genoma humano', in *La moral cristiana como propuesta* (San Pablo, Madrid, 2004), pp. 477-510.

MAURIZIO PIETRO FAGGIONI

7.The Ethics of Genetic Counselling

The expansion of scientific knowledge in the genetic field and the new diagnostic possibilities that exist raise the question of whether to place people – both individuals and couples – in a condition to know whether there exist reasons for carrying out genetic tests on themselves and on their children. Once a diagnosis has been made it is also necessary for those involved to understand the meaning of the level of reliability of that diagnosis, for them to be informed about possible therapies, and for the possible risks connected with their choices in the field of reproduction to be clarified. Accompanying people in this field is so delicate and complex in character that it is the task of genetic counselling. The extremely varied typology of the possible situations allows only a general and summarising picture of the principal ethical aspects of genetic counselling to be given here.

1. Pre-marriage Counselling

A first and fundamental typology is pre-marriage counselling. Indeed, the possibility exists to identify the asymptomatic carriers of pathological traits before they transmit these traits to their offspring. Subjects or couples with the risk of having a genetic illness are studied from the point of view of family anamnesis (retrospective counselling) and their present state (prospective counselling). Once the diagnosis has been made it is the task of counselling to inform those involved about the nature of the pathology of which they are the carriers and of the risks that exist for their offspring.

The fundamental ethical requirement of counselling is the truth. However, one is not dealing here with solely scientific truth, truth that is cold and detached, because this truth can upset the existence of a person or a family group. One is dealing with human truth that should be communicated within the context of a dialogue based upon trust, loyalty and sincerity and which is able to respect the times and the reactions of each person. The creation of excessive alarmism, like the minimisation of objective risks, are unacceptable approaches that do not provide people with a good service.

The aspect of counselling that relates to choices in the field of reproduction is of a delicate nature. In our pluralistic and relativistic cultural context much emphasis is placed upon the 'value neutrality' of counselling. Obviously enough, the task of counselling is not to produce this or that choice but to lead the couple to consider the concrete risk of transmitting a genetic disease and to become aware of the consequences of their choices for their offspring and themselves. Although, however, an approach of not directing meets the needs of respecting the freedom of the patient, on the other hand non-directive counselling is often not totally adequate in helping people who are the carriers of genetic diseases to address certain more difficult choices. Educational counselling has been shown to be useful and this envisages a more active role on the part of counsellors who try to help the couple to focus in a precise way on the motives that lead to certain choices about pregnancy and to identify the existential meaning of various types of choices – from simple neutral information one passes here to a clarification of the values of the patient. In the light of the existential values of the couple, one can realise whether they underestimate the seriousness of the risk, whether the responsibilities that come from the procreation of a sick child have been seriously assessed, and whether the wish exists to accept and, whatever the case, look after the child.

Whatever the case, nobody has the right to take the place of the conscience of the couple or apply pressure in relation to such a personal decision, even though, not rarely, there are undue intromissions by health-care workers who, in the case of a diagnosis that has turned out to be positive for a transmissible disease, suggest, employing very pressing advice at the limits of psychological terrorism, that a pregnancy should be avoided at all costs. In many countries, an ancient form of medical paternalism which is hard to die, and a very widespread eugenic impetus, lead a by no means a few health-care workers to invade what should be the field of the informed and free choice of the couple with so-called 'indications'. In counselling, the subject of social responsibility in preventing the spread of genetically transmitted diseases can come into conflict with the thought-through motivations of the couple in favour of procreation, and authentic neutrality can be transformed into a directive approach based upon eugenic thinking which is often unconscious and veiled.

Pre-marriage diagnosis and the foregoing of procreation represents today the only ethically acceptable possibility by which to avoid the transmission of genetic diseases that do not respond to therapy. An approach which advises against transmitting life when there exist serious risks of bringing into this world a creature who is gravely damaged at the level of his or her physical or mental integrity appears, in fact, more in conformity with a vision of responsibility towards life. This generally negative approach, however, is not translated into a prohibition – the right of every couple to decide to procreate with an aware shouldering of their own responsibilities remains in force and a choice in this direction must also be respected at a practical level by assuring all the forms of help that are necessary to the couple and to the conceived child.

This, in essence, was the teaching that Pope Pius XII formulated as early as the 1950s: 'There certainly exists the motive and in most cases the duty to warn those who are certainly the carriers of grave hereditary diseases of the burden that they are about to impose on themselves,

on their partners, and on their descendants. This burden may perhaps become unbearable. But to advise against is not to prohibit. There can be reasons, above all of a moral character and a personal kind, of very great importance that authorise the contracting and employment of marriage in these circumstances as well'.[1]

Although, lastly, it is true that the carrying out of a pre-marriage or pre-conception test meets a sense of responsibility towards life, it should also be emphasised that these tests cannot be imposed by law, nor should they be considered morally obligatory. It is the task of the bodies responsible for health-care policies to try to engage in a work of sensitisation in relation to young people, above all in relation to those contexts and categories that are most at risk as regards certain genetic pathologies.

2. Counselling in Prenatal Diagnosis

A second major chapter is that of prenatal diagnosis, both during pregnancy and before implantation where the techniques of *in vitro* fertilisation are employed.[2] Prenatal diagnosis is a medical act that cannot be engaged in with the sole aim of reducing the anxiety of the parents. It must be carried out only if there exist precise *indications* ascertained by preventive counselling and codified in the international literature in the field. Unfortunately, the strong pressure of the mass media, the secret desire for a perfect child, and the increasing availability of genetic tests for even very rare diseases are increasing beyond any reasonable limit the requests for this kind of service. Given the large number of hereditary diseases, counselling should first and foremost dispel the illusion that people have that it is possible to detect the existence of all genetic diseases in the unborn child and also persuade people that the absence of certain pathologies tested for in the foetus does not allow it to be stated with absolute certainty that the foetus involved is 'healthy'.

In holding up the possibility of a prenatal diagnosis, the consultant should in addition bear in mind the risks run by the mother and the child and above all the risk of a miscarriage that is connected with these invasive techniques, such as amniocentesis and villocentesis, a risk that increases the earlier the test is carried out during the pregnancy. The Instruction *Donum vitae* states that 'such a diagnosis is licit if the methods employed, with the consent of the adequately informed parents, safeguard the life and the integrity of the embryo and its mother, and does not make them run disproportionate risks'.[3] On the basis of the principle of proportionality, an invasive diagnosis should be employed solely in the case of a medical indication to that effect and one should also establish whether the risk of a miscarriage is counterbalanced by adequate benefits for the unborn child. Indeed, it would not be just to have the unborn child run a risk if a benefit could not be reasonably hoped for in relation to that child and the only possible benefit was a psychological benefit for the mother. For this reason, when prenatal therapeutic prospects do not exist it is licit to ask oneself whether a genetic diagnosis has a purpose and whether the benefits for the unborn child are really greater than the risks, taking into account that one is dealing with the risk of a miscarriage.

Not even the introduction of non-invasive prenatal diagnostic tests will solve all the problems involved. The relative simplicity and innocuousness of certain tests, such as that involving exploration of foetal cells and DNA in the blood of the mother, could increase the requests for diagnosis with accompanying lesser control over the real medical indication. The chance character and the many false positive results of these and other tests, such as the triple test for Down's syndrome, will have the effect of increasing the number of tests involving amniocentesis that are engaged in to establish and confirm a hypothesis at the level of diagnosis, in women who would not otherwise be candidates for amniocentesis as well. Thus the field of non-invasive prenatal diagnosis also brings out the irreplaceable role of counselling. In general, the moral criterion applies which lays down that one should choose that method that involves less risk and has the greatest reliability and precocity.[4]

A frequent moral dilemma to be found in the field of counselling is that of the possibility of an abortion when a grave genetic pathology has been detected in the unborn child. The ethical aspect does not change substantially according to whether one is dealing with sick embryos identified by means of pre-implantation diagnosis or with embryos that are already in the womb. The question arises of whether the consultant should share in the intention to have an abortion of the person who asks for the prenatal diagnosis. Indeed, prenatal diagnosis, as *Donum vitae* teaches, 'is gravely in contrast with the moral law when it contemplates the possibility, depending on the results, of procuring an abortion'.[5]

Although the diagnostic act is to be located within screening programmes on a large scale directed towards identifying and eliminating sick embryos and foetuses, the possible co-operation in this of the consultant, whatever his or her viewpoint may be, is not ethically acceptable. The case is different when the consultant does not agree personally with the intention to engage in an abortion of those who a make a request for such a diagnosis but, rather, respecting their autonomy, strives to lead those involved to a more objective assessment of the situation which takes into account the value of unborn life that is entrusted to their responsibility. A disquieting aspect of contemporary culture is precisely discrimination towards the most fragile existences, which are placed at the margins of the moral community and held to be without value and rights because they are adjudged to be lives of too low a quality. Counselling can in this case become an instrument of the dangerous eugenic decline of a part of contemporary medicine or, conversely, it can be a privileged moment of a form of medicine whose primary purpose is to help and support sick

life and not fight it as though it were an enemy. Only in going decisively in this direction can counselling conjoin the values of respect for informed truth and autonomy with the fundamental value of respect for life and above all for that life that is most undefended and wounded.

3. Towards a New Form of Medicine

The advances in genetics, in its various and complex expressions, are opening up a path towards a new model of medicine, that of predictive medicine.[6] Hitherto, diagnosis has amounted in substantial terms to ascertaining the present state of health of a person. Predictive medicine, on the other hand, allows and will increasingly allow the prediction – with varying degrees of certainty – of the pathologies that could develop in a person in the future.

Today in many cases it is already possible to predict beforehand the emergence of monogenic hereditary diseases whose signs come out in a clear way only late during a lifespan or to ascertain the presence in a person of a predisposition of varying levels of clarity to the development of specific physical and mental pathologies whose outbreak depends on a series of joint causes. We will have to increasingly learn to manage diagnoses with a component of uncertainty to which we are not yet used, we will have to think anew about medical knowledge in terms of probability, and we will have to increasingly develop strategies of prevention designed for specific individuals on the basis of their own dispositions.

When genetic information on every citizen is available and sufficiently reliable, the serious problem will arise of the management of these data. There will be new problems for the defence of privacy caused both by the organisation of health-care data banks, including genetic data banks, and by the concerns of insurance companies and employers about the future state of health of their customers and their employees. In the personalist approach there prevails the view that the genetic profile of each person is a personal good and that knowing about it by third parties has to be justified on therapeutic grounds and that, whatever the case, every communication of these data must be explicitly authorised by the person concerned. The Convention on Human Rights and Biomedicine of the Council of Europe stressed that 'one cannot engage in predictive tests for genetic diseases or tests that allow the identification of a person as a bearer of a gene responsible for a disease in order to discover a predisposition or a genetic susceptibility to a disease, unless this is done for medical purposes or medical research and subject to adequate genetic consultation'.[7] In this perspective the programmes involving the genetic screening of new born children that are being launched in many countries, above all for diseases such as cystic fibrosis and certain haemoglobin illnesses, must also be assessed ethically.

Given the gap between potentialities at the level of diagnosis and possibilities at the level of treatment (the so-called 'therapeutic gap'), one wonders, lastly, what kind of life can be led by a person who comes to know at a young age that with a very high probability or even with certainly he or she will develop a pathology.[8] Let us take the case of Huntington's Chorea, a grave neurological disease that is potentially fatal and is inherited as a dominant autosomic tract but which emerges only at a late stage of life. How can a young person plan his or her future, dedicate himself or herself to studies and work, marry, and have children, knowing that his or her life is rapidly moving towards a fatal outcome?

The temptation to conceal such information which is so disturbing and able to disrupt the life of a person is great, above all for those parents who would like to spare their child a life lived out in anxiety. A truth projected too far ahead in time could turn out in the end to be inhuman because it is unsuited to human rhythms, to human capacities to plan, to the human need to hope in the future, but it is also certain that the right to know the truth about oneself is a right rooted in the person and in that person's dignity as a free and responsible being. There will be an increasing number of truths which today we are not yet prepared to receive and live out but which we must increasingly learn to address. This opens up new moral problems for those who are called to offer their help through genetic counselling.

I do not believe that I am emphasising the point too much if I say that the task of counselling, beyond the necessary medical-scientific skills and expertise, will increasingly require more ethical capacities: indeed, in simpler and greater terms – human capacities.

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Note

[1] PIUS XII, 'Discorso al I Simposio Internazionale di Genetica Medica, 7 settembre 1953', in *Discorsi e Radiomessaggi*, vol. 15, (Vatican City, 1954), p. 264. Cf. PIUS XII, 'Discorso al VII Congresso della Società Internazionale per la Trasfusione del Sangue, 5 settembre 1958', *Acta Apostolicae Sedis*, 50 (1958), p. 732: 'Better instructed in relation to the problems raised by genetics and the gravity of certain hereditary diseases, the men of today, more than in the past, have the duty to take into account these acquisitions in order to avoid for themselves and other people many difficulties of a physical and moral character. They must be careful about everything that could provoke permanent damage in their descendants and drag them into an interminable series of sufferings'.

[2] DI PIETRO, M. L., GIULI, A., and SERRA A., 'La diagnosi preimpianto', *Medicina e Morale*, 54 (2004), 469-500; SERRA, A., 'La consulenza genetica prima della diagnosi prenatale: un obbligo deontologico', *Medicina e Morale*, 47 (1997), 903-921. It is almost superfluous to observe that the techniques of extra-corporeal fertilisation should not be considered illicit but the pre-implantation selection of embryos that have been fertilised *in vitro* adds the perverse malice of those who, after giving life, take it away in the name of the quality of the result.

[3] CONGREGATION FOR THE DOCTRINE OF THE FAITH, Instruction *Donum Vitae*, I, 6, *Acta Apostolicae Sedis*, 80 (1988), p. 79.

[4] BENCIOLINI, P., and VIAFORA, C., (eds.), *Etica e ostetricia. Il Triplo Test* (Rome, 1998) (*Quaderni di etica e medicina* n. 5).

[5] CONGREGATION FOR THE DOCTRINE OF THE FAITH, Instruction *Donum Vitae*, I, 6, *Acta Apostolicae Sedis*, 80 (1988), p. 80.

[6] FINKLER, K., SKRZYNIA, C., and EVANS J. P., 'The new genetics and its consequences for family, kinship, medicine and medical genetics', *Social Science and Medicine*, 57 (2003), 403-412; HOLTZMAN, N.A., and MARTEAU, T. M., 'Will genetics revolutionize medicine?', *New England Journal of Medicine*, 343 (2000), 141-144; VINEIS, P., SCHULTE, P., and MCMICHAEL, A. J., 'Misconceptions about the use of genetic tests in populations', *The Lancet*, 357 (2001), 709-712.

[7] THE COUNCIL OF EUROPE, *Convenzione sui diritti dell'uomo e la biomedicina*, Oviedo 4 April 1997, art. 12.

[8] DUNCAN, R.E., SAVELESCU, J., GILLAM, L. *et al.*, 'An international survey of predictive genetic testing in children for adult onset conditions', *Genetics in Medicine*, 7 (2005), 390-396; HEINRICHS, B., 'What should we want to know about our future? A Kantian view on predictive genetic testing', *Medicine, Healthcare and Philosophy*, 8 (2005), 29-37.