Gene Therapy, Yesterday and Nowadays

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INTRODUCTION

In our previous chapter 5 we have commented on some implications of the economic interests presence in the development of the Human Genome Project and on some of the applications of this latter in the biomedical field, paying special attention to the tests for genetic diseases diagnosis in general and to the multifactorial ones in particular.

The present chapter will be devoted to the gene therapy, one of the fields which has aroused more expectations in the last few years, since, unlike the above referred diagnostic tests, the gene therapy is directed not to the diagnosis but to a cure of diseases that, by means of its application, claims to become definitive. Although the investigation of gene therapy has been developed in parallel with the Human Genome Project and cannot be considered its direct consequence, there is no doubt that the knowledge of the whole sequence of the human genome, as long as it allows the knowledge of all the genes, can suppose a very important impulse for the possibilities of the gene therapy[1].

In this chapter we will describe what the gene therapy consists in, the main steps it has taken so far from its launching and some of its present and future applications. We will also discuss the most important problems it meets and why, in spite of these, it constitutes one of the greatest hope for medicine that the biotechnological revolution has brought in the last twenty-five years.

DEFINITION AND TYPES OF GENE THERAPY

There is not only one satisfactory definition of gene therapy. Lacadena presents two of them, one more strict and the other wider:

In the strict sense by human gene therapy (GT) we understand the deliberate administration of genetic material in a human patient with the intention of correcting a specific genetic defect. Another wider definition considers the gene therapy as a therapeutic technique by means of which a functional gene is inserted in the cells of a human patient in order to correct a genetic defect or to provide the cells with a new function.[2]

The first definition, the more strict one, corresponds to the first protocols of gene therapy of the early 90s, i.e., clinical trials directed to correct the effects of some recessive monogenic diseases. However, this definition does not embrace a good part of the procedures that, in an experimental level, are starting to be testing in animal models and even in humans. Adopting the second definition can help solving this problem but it reveals the contrast: when we excessively extend the limits of the concept some problems of perhaps greater social importance appear. Some authors have warned against a too lax use of the concept of gene therapy since it can pave the way for treatments which are not properly therapeutic but they are presented as if they were. They point out, besides, that this wide use of the concept is not innocent and it can be considered a way to make more acceptable the procedures of human genetic engineering which otherwise could have a greater social opposition. In this sense, Miguel Moreno states that:

We should not consider gene therapies the ones destined to prevent the development of hereditary diseases, in accordance to the data derived from a genetic analysis revealing of tendencies to these diseases; neither the ones of preventive nature, against widespread infections of viral origin; or the gene transfers destined to identify the (genetic, physiologic, chromosomal, etc.) phenomena involved in the etiology of a specific disease (its first aim is the diagnosis, which is useless for the therapy on numerous occasions).[3]

Bearing in mind these considerations, although this does not completely satisfy the purpose of our discussion, we will use all through this chapter the generic definition according to which the gene therapy consists in the genetic modification of cells in a patient in order to fight a disease[4]. Although it does not completely eliminate the aforementioned problems, it restricts the use of gene therapy to properly therapeutic purposes and leaves out diagnostic, preventive or eugenic uses not properly curative. Besides, a so general definition allows to embrace very different strategies designed to the cure, by means of genetic techniques, of not only genetic diseases but also infectious ones.

Another problem we have to bear in mind when

we refer to gene therapy is its fundamentally experimental character. In this sense, defining it as a therapy is only a projection of future potentialities that at the moment have expressed themselves in only one case[5]. Excepting this case, the most successful clinical trial which have been made so far, gene therapy must be considered more as a treatment, which has lead to a temporal improvement, than a cure as such[6].

Depending on the kind of cells to which it is applied, we can distinguish between somatic and germinal gene therapy[7]. The first one directs the genetic modification to any of the patient's somatic tissues and, although it could have lasting effects, it is restricted to the treated individual. Under no circum-stances these changes pass to the descendants because the genes which are transmitted from parents to children are those present in the ovules and spermatozoids. A genetic intervention on the lung, nervous, muscle, blood or hepatic cells, just to give a few examples, could correct genetic defects in these tissues or organs, but these cells are not transmitted to the progeny and for this reason, although it could become very important for the patient in question, it lacks hereditary consequences.

The germinal therapy, on the contrary, would be directed to the genetic modification of reproductive cells or of their precursor cells in the germinal line or of the embryonic cells in the first steps of development. In the case of germinal cells, the therapeutic effects would manifest themselves over the descendants originated from the germinal treated cells, but not over the individuals who produce these cells. Since they affect the germinal line, only the offspring of the individual who underwent the therapy will present and spread for inheritance the change to the following generations. At the moment, the germinal therapy is not authorized in any country and all the protocols used in human beings are currently related to somatic therapy[8]. However, as the social and ethical consequences of the application of these two types of therapies are very different, the debate about the future use of the germinal therapy has considerable relevance: that is why we will deal with it, although briefly, at the end of the chapter.

Regarding the methods of application, we have to distinguish the *ex vivo* therapy, when the genes are transferred to the patients' cells kept culture, which will be subsequently reincorporated to the organism, and the *in vivo* therapy, when the genes are transferred to the patient directly[9], for example, through the blood stream. A variant of the last one is the *in situ* therapy, if the treatment is executed directly in the affected organ[10].

From a theoretical point of view, different strategies of gene therapy can be conceived depending on the objective pursued[11]. The simplest and most common one consists on the *gene insertion*, the introduction of a normal gene copy in the treated cells. This technique, also known as *gene augmentation therapy (GAT)* due to the effect it produces[12], is applied to recessive diseases in which the normal genetic product is not manufactured. The introduction of a copy of the gene non mutated variant aim to the production of the functional protein in a quantity enough to re-establish the normal phenotype. In this procedure the mutant recessive genes do not interfere with the normal genetic product and for this reason it is not necessary to eliminate it. The gene insertion is especially suitable for recessive diseases that do not require a strict regulation in the quantity of genetic product manufactured for the normal phenotype to be recovered. That is why it is the more often used gene therapy technique and practically the only one tested in the protocols with human cells affected by hereditary diseases. However, it is useless for almost the whole of the diseases produced by genes of dominant effect.

A second kind, more difficult from the technical point of view, is the *direct correction of mutations (gene targeting)* by means of any modification procedure or genetic surgery which can either replace the defective gene with a normal copy of the same one or only replace the mutated sequence of the gene with the normal sequence, recomposing in this way the original function of the gene. The specific mechanism for this substitution would be the homologous recombination[13], that has already been tested in mice but, due to its difficulty and the current little reliability, it has never been tested in humans yet. It would also be possible to make the correction at the RNA level by means of the use of ribozymes. If this method was applied, some dominant diseases could be treated.

There are other strategies of gene therapy as the *direct suppression of the specific cells* inserting suicide genes or genes which stimulate the immune response or the *direct inhibition of the gene expression* blocking the DNA, the RNA or the protein produced by the gene. There are several possible methods to get this objective, as it can be use antisense DNA or the formation of triple helixes by means of DNA oligonucleotides. The methods based on the suppression of cells have been already tested in order to eliminate cancerous tumours, while the one based on the inhibition of the gene expression could be useful for the treatment of certain types of cancer,

some infectious diseases and for hereditary diseases of dominant effect.

With a so large catalogue of gene therapy techniques, the spectrum of diseases which could be treated is theoretically quite extensive. Among them there are infectious diseases, cancers, recessive and dominant hereditary diseases and disruption of the immune system, as allergies and auto-immune diseases[14]. Instead, in practice, the difficulties to successfully apply the most important part of gene therapy strategies are numerous and the results obtained so far have been much more modest than they were expected at the beginning. The problems can arise because of the nature of the treated disease, the kind of tissue the problems is located in, the method used to transfer the genes to the cells or, even, the control level of the gene expression necessary for the treated cells to normally work. There are some cases of immune reactions against the normal genetic product manufactured by the gene introduced by means of a therapy, which the organism consider strange.

APPLICABILITY CONDITIONS OF THE GENE THERAPY

Although the gene therapy could be theoretically applicable to very different diseases, as we have just seen, there are several factors that condition its applicability and have enormously reduced the concrete possibilities of action.

The first of these factors concerns the type of inheritance. In general, Mendelian diseases, determined by the action of only a gene, are better candidates than multifactorial diseases that, besides their dependence on the whole action of several genes, are influenced by environmental factors. An exception to this general criterion is cancer that, although it can be considered a typically multi-factorial disease, has been the object of the greatest number of protocols of gene therapy in the last few years.

The second factor to consider is the pattern of inheritance. Recessive diseases are better candidates for gene therapy than the dominant ones. In the former, due to their recessive character, it could be sufficient to add a copy of the healthy gene to recover the normal phenotype, whereas in the latter this is not sufficient in the majority of the cases and it would be necessary to turn to some kind of modification of the damaged gene, enormously complicating the possibilities of intervention.

The third factor refers more specifically to the nature of the mutation which causes the disease. For example, when there a loss of function mutation, i.e., the affected gene stops producing the encoded protein or it is not functional, as in the majority of the recessive diseases, the defect could be corrected by means of gene augmentation therapy; this therapy, in fact, is the simplest of all, since, at the beginning, the introduction of a normal copy of the gene to produce the functional protein would be sufficient. On the contrary, the gain of function mutations, as the appearance of a new mutant protein of a toxic product, which are characteristic of some dominant diseases, cannot be treated adding normal genes and would need other strategies which are more difficult to carry out, like the specific blocking of the mutated gene or the direct correction of mutations (gene targeting).

The fourth factor to take into account is the control of the gene expression. Those genes which do not need an excessive control of their expression, keeping a functional phenotype with variable levels of genetic product, are the easiest to treat. On the contrary, when the gene expression requires a strict control the problems are much bigger. This has been the case, for example, of the erythrocytes disease α-thalassemia treatment by means of gene therapy. The expression of the α-globin inserted gene requires, in order to cure the disease, an exact control of its production, which must be equal to the one in the α-globin. This is necessary for the resultant molecules of hemoglobin, formed by two protean chains of α-globin and two of α-globin, to normally carry out their function. This need of controlling the gene expression has impeded, so far, to attain significant progress in the application of gene therapy to this blood disease.

The fifth important factor in the applicability of the gene therapy is the size of the gene coding DNA to insert. The genes with small size sequences are always better candidates, whereas the genes with a big size coding DNA can be difficult to transfer to the inner part of the cells due to the difficulty to find suitable vectors.

Lastly, the disease will be more easily treated if it manifests itself in a tissue whose cells can be removed, easily cultivated *in vitro*, resistant to manipulation, and reintroduced without difficulty in the organism. Besides, it would be desirable that the cells could have long life, for the whole life of the patient if possible. The cells that approach most to these tissular conditions are, above all, the ones in the bone marrow, the skin and the liver and for this reason they would be the best candidates.

The more often used standard procedure of gene therapy follows, in a briefly way, these steps[15]: 1)

Identification, isolation and amplification of the gene which is going to be used for the treatment; 2) Removal and in *vitro* cultivation of the cells of the treated tissue; 3) Transfer of the therapeutic gene to the inner of the cells by means of a vector. The transferred gene must take a promoter sequence which allows its expression and must also be accompanied by some markers which allow the identification of the cells to which the gene has been incorporated, for example a gene resistant to a particular drug. In this way, when the culture is exposed to the drug in question, the only ones which will survive are the most resistant ones, i.e., the ones which have incorporated the resistant gene and the therapeutic gene associated to it. Next, the selected cells with the gene incorporated are transferred to the patient where they exert the normal physiological function which would lead to the elimination of the pathology.

One of the crucial steps which has created many problems so far, has been selecting the suitable vector for the gene transfer. The main kinds of vectors are viruses (retrovirus, adenovirus, adeno-associated virus, herpesvirus and leintvirus, a particular group of retrovirus), although tests with liposomes, molecular combined and naked DNA have been also carried out[16]. The use of viruses as vectors in gene therapy is carried out destroying the pathogenic activity of the virus and its capacity of multiplication inside the cells. In order to do it, the genes responsible for these functions are eliminated from their DNA, and replaced by the therapeutic DNA fragments which are going to be transferred. Each kind of vector presents advantages and disadvantages and, so far, none of them has turned out to be suitable[17]. Retroviruses and adenoviruses are the most used vectors now and due to the non technical character of this exposition they will be the only ones we will briefly comment on.

Retroviruses present high effectiveness in gene transfer and have the advantage of integrating the transferred DNA in the chromosomes of the treated cell, offering stability in the long term. However, they present some important problems. The most outstanding one is that integration of the transferred DNA in the chromosomes of the cell is made by chance and it could interfere in the operation of a healthy gene. It could even turn the cell into a cancerous one if the insertion is made in a proto-oncogene or in a tumour suppressor gene. Secondly, they can only transfer DNA to the cells which are actively divided and so they are not suitable for those tissues where the cells are not usually divided as the nervous or muscle tissue. Thirdly, they cannot be used for the *in vivo* therapy since they are normally eliminated by the immune system of the complement. And, finally, the transferred DNA cannot exceed the size of 8 kb (8,000 nucleotides) that is why they are not of use to transfer too big genes.

As for adenoviruses, viruses which in their natural state provoke common colds, their main advantages are that they also present high efficiency in gene transfer, they can carry big genes, until 35kb, and can infect cell which are not divided. Besides, they are suitable to make *in vivo* therapy, since they can be transferred directly to the patient's tissues. The main disadvantage lies in the fact that they do not integrate the DNA in the chromosomes; this is the reason why their effect is not lasting, since the genes are lost when the cells are divided. In some cases this problem could become an advantage if the effect they pretend to get is transitory as in the case of some protocols of the gene therapy against certain types of cancer. Another problem they present is that they usually provoke an important inflammatory and immunological response, which can arise complications in the patient. Besides, this immune response reduces the efficiency of the therapy, on eliminating a fair part of the viruses which are used for the transfection.

At the moment, the question of gene transfer vectors is one of the most important technical problems which gene therapy presents and has limited so far the obtaining of satisfactory results that some researches believe that the future strategies will have to change substantially: "Almost for certain, the tools of the future are not going to be the prototypes which are being tested in the laboratories nowadays. And there will not be an ideal technique for each disease, but there will be a lot of options"[18].

PAST AND PRESENT OF THE GENE THERAPY

The first clinical trial in gene therapy carried out in human beings goes back to 1980 when Martin Cline made an attempt to cure two thalassemia sufferers by means of this technique, without their previous permission[19]. The attempt was not successful and ended in Cline's loss of his position.

The approval of the first clinic protocol for a trial test which implied the insertion of a gene in a human being was made in January 1989. It was presented by the Doctors Anderson, Blaese and Rosenberg and it was not a gene therapy properly[20]. In September 1990, the same Blaese, Anderson and

their collaborators carried out the first clinical trial in gene therapy with a successful result. The patient was a four years old girl with deficiency in adenosine deaminase, a very rare recessive disease which provokes a serious combined immunodeficiency[21]. The treatment consisted in introducing the ADA gene in cultivated T lymphocytes extracted from the patient, and later reintegrating them into the organism. Since lymphocytes are not stem cells and have a temporal limited duration it was known that, even in the case that the test was successful, the cure would not be definitive and it would have to be repeated at regular intervals. Although the results were positive and the girl could lead a normal life since then, the treatment had to be repeated, first every 1-2 months and subsequently every 3-6 months. However, it is difficult to make a precise evaluation since the patient was simultaneously treated with PEG-ADA, a drug which includes the normal protein ADA and is used in the conventional treatments of this illness[22]. Since then more than 3,000 patients have had gene therapy for several complaints all over the world.

In 1992, the clinical trials included, besides the transfer of the ADA gene to lymphocytes, the transfers of six more different genes, some of them related to tumours[23]. Tests for some hereditary disorders such as cystic fibrosis, familiar hypercholesterolemia, Gaucher disease and Duchenne muscular dystrophy have been made in the last years. Until August 2000, in the National Institutes of Health of the United States there were 431 gene therapy tests of which 393 (91 per cent) belonged to the United States and 38 (9 per cent) to the rest of the world[24]. Among them, 271 (64 per cent) were devoted to cancer, 33 (9 per cent) to AIDS, 28 (7 per cent) to cardiovascular diseases, 25 (6 per cent) to cystic fibrosis and the other 52 to other diseases, none of which separately exceeded the 2 per cent of the tests altogether[25].

From these data a strong predominance of the tests designed to treat cancer and, in quite smaller proportion, to AIDS stands out. Various authors[26] agree to say that the reasons of this preponderance of gene therapy tests about cancer result from several factors among which we count, besides the seriousness of the illness: the greater ease of the treatment by means of gene therapy than other diseases "because programming a destructive strategy directed to the elimination of the cells is easier than a constructive one designed to restore its correct functioning"; the great experience existing in investigations on tumours from the clinic point of view; the huge financing which are destined to cancer investigation and the interest of the pharmaceutical industry on a problem which affects such a great number of people. However, "in spite of this effort, and as it was expected due to its complexity, cancer is proving to be a disease which is very difficult to be corrected, and progress in this area has been modest"[27].

Until nowadays, the only case of (provisionally) definitive recovery registered by means of gene therapy has been achieved by Marina Cavazzana-Calvo and Alain Fischer at Necker Hospital in Paris[28] on treating five children suffering from severe combined immunodeficiency. Unlike other previous cases, in this occasion stem cells extracted from the bone marrow were cultivated and the functional gene was inserted in them by means of a retrovirus. The cells were reinjected in the patients' bloodstream five days later. After three months the treated children had recovered their body's defence system and four of them could live with their families again with no additional treatment[29]. Having made the treatment in hematopoietic stem cells and not in previously differentiated cells has allowed the therapeutic effect to be permanent, since the cellular renovation is made out from stem cells corrected by means of gene therapy.

PROBLEMS OF GENE THERAPY AND OF ITS APPLICATIONS

In spite of this achievement, the advances in the gene therapy tests carried out have been limited so far and the results are quite modest. Besides, in the last three years suspicion about the security of the tests has been generated by the death of a patient (Jesse Gelsinger, aged 18), published in 1999, as a consequence of the gene therapy treatment which he was being submitted to, to try and cure the ornithine transcarbamilase deficiency he was suffering[30]. According to the official investigation made, "the researches concealed crucial information which could have prevented the incident [...]. Besides the scientists had concealed from the FDA that other two volunteers previously subjected to the same test had suffered so serious side effects that, if they had been notified, they had meant the immediate suspension of the test, according to the rules previously agreed by the scientists of the FDA"[31].

After this case, and as a consequence of the alarm provoked by it, news of other concealment of problems and up to nine deaths not notified were published[32]. The director of the Scientific Policy

Office of the USA informed that in 1999 "1,070 adverse incidents occurred in tests, of which only 39 were notified to the NIH"[33]. The majority of these cases of concealment seem to have had "purely economic reasons. Scientists kept quiet not to lose the financing of the Pharmaceutical companies, and these ones at the same time demand silence about their products"[34]. If this causal relationship between the concealment of the adverse results (including serious risks for people) and business interest is true, we will be in the presence of one of the most negative consequences that can be derived from the pressure of the private economic interests on biomedical researches potentially beneficial for the population; and, moreover, this can become not only harmful for their direct consequences over the affected people, but also for the discredit it brings on the whole research on human molecular genetics. In this sense the American Society of Gene Therapy has proposed that scientists should not be responsible in the projects which have economic interests[35].

For these reasons it is necessary to deal with the problems of gene therapy with transparency and a strict control over the protocols to be tested, putting aside the excess of triumphalist propaganda which, in a self-interested way, has characterized the public information related to the gene therapy. There is a broad agreement on the fact that, if scientists and researchers take the demanded precautions for every new therapeutic treatment in experimental stages, the somatic gene therapy will not create ethical problems different from those of other more conventional treatments[36], as in the case of the organ transplants. Miguel Moreno summarizes this assessment shared at great length:

The therapy by gene transfer in somatic tissues creates very limited ethical questions, since the success or the failure in the attempt will affect only to the sick patient. It would raise worries typical of any kind of experimentation with humans, i.e. the calculation of benefits and risks for the individual. There is unanimity in requiring a detailed evaluation of the risk which implies the use of viral vectors, including their capacity to infect the progenitor's cellular lines and the potential collateral damage of the insertion.[37]

The problems denounced so far, which have called on the reliability of the gene therapy into question, are precisely related to the detailed evaluation of the risk referred to in the above quotation, with transparency in the notification of the results and with the necessary control on the part of scientific and ethical commissions of evaluation. Partially following Lacadena[38], we can summarize the current ethical requirements in somatic gene therapy in the following points: 1) Gene therapy should be only applied to treat patients with serious diseases; 2) It should be tried only when there are no other therapeutic alternatives or, if there are others, they suppose a bigger risk or a less beneficial action; 3) Its application to a human disease should require the evidence that it is sure, beneficial, technically possible and ethically acceptable; 4) With the precedent conditions, the somatic gene therapy for the treatment of serious diseases can be considered ethically accepted because it can be supported by the fundamental principles of autonomy, charity and justice.

In my opinion it is positive that, despite the problems we have pointed out and with the necessary safeguard, the gene therapy investigation and its therapeutic potentialities goes on developing, because in the future beneficial results from the medical point of view, unattainable by other ways, can be obtained for a certain number of diseases. However, even completely accepting the necessity of the somatic gene therapy development, there is no harm in wondering why its possibilities in the long term were exaggerated and excessive or even simply unfounded hope was deposited in it. This excess of trust does not consist only in a popular belief coming from ignorance of the real gene therapy problematic. The scientific community itself has been in charge of fostering this confidence in its imminent therapeutic capacity. We have already pointed out that one of the underlying reasons could be the necessity of financing the research and the economic interests of the enterprises which support them. But there are also ideological type of reasons which reinforce this tendency for search of genetic treatments, of doubtful usefulness in some cases, underestimating or even consigning to oblivion other important lines of investigation.

In this sense, we have commented in the previous chapter on the weight that the predominant biological determinism ideology had in the applications of the genetic diagnosis tests and in the strategies of fighting cancer; the funds devoted to epidemiological studies, for example, are definitely small compared to the ones destined to genetic studies[39].

This same tendency to attach too much importance to the researches designed directly to the action on the genes is revealed in the expectations set in the gene therapy, as if always and in every kind of disease this therapeutic action was more efficient than

any other alternative strategy. In this way the study of the causes, not only genetic, which favour the raising of many diseases, determinant for the effort to reduce their incidence, is, in practice, underestimated.

We must not forget that when we are referring to the causes of the diseases, in most of them the genes constitute one of the causal elements, but are seldom the only one. The case of multifactorial diseases, like cancer, where genes and environment interact in a complex way is the most notorious. But even in some metabolic diseases caused by the mutation of only one gene, the factors which had an influence in the manifestation of the disease can be various. The case of phenylketonuria is, doubtless, the most well-known. This ailment is produced by a recessive gene which is expressed in the homozygotic individuals, who receive both genes from their healthy bearers parents. The phenylketonuric individuals are unable to metabolize the phenylalanine amino acid and turn it into tyrosine. Phenylalanine accumulates in the cells causing alterations like mental retard. But if this individuals are provided with a diet almost lacking in phenylalanine[40] and supplemented with tyrosine from the very moment of their birth until the end of the period of growth, the development can be normal.

This case illustrates how internal facts (genes) and external ones (the diet in this case) contribute to determine the development or the absence of the disease. There are other genetic diseases in which the action of the genes turns out to be much more influential or even completely determinant. In Duchenne muscular dystrophy or in Huntington's disease, to quote just two well-known cases, the action of the deleterious genes cannot be counteracted by means of other treatments and the gene therapy, when it will be available, can represent the only hope of recovery for the people who suffer them. However, in other cases the gene therapy, although it could be possible, would not be always the best strategy to use, especially if we deal with multifactorial diseases.

Firstly, because the action on environmental factors, besides being efficient, can contribute to a very important preventive action, which would reduce the cases in which the disease could develop. Secondly, because other treatments different from the gene therapy can be more recommended, even if the disease has a well established genetic base. But nowadays, despite its limited current therapeutic potential, researchers in human genetics are usually heading for the gene therapy, even before assessing other more conventional hopeful ways. This fact was highlighted in the report ordered by Harold Varmus, director of the NIH, to an *ad hoc* committee of fourteen experts where it was said that "the researchers jump immediately, in some cases, from the discovering of the gene bound to disease to the gene therapy, without previously use the discovery as a base of work for more conventional treatments"[41].

This state of things related to the hope aroused by the gene therapy would be a sign of what some authors have called the "genetization" of society or the "mystification of what is genetic". Jacques Testart, one of the most critic scientists in this sense, thinks that "the gene therapy appears perhaps as a gigantic *bluff*, nurtured by the economic appetite of the industrials, by the pride of the researchers, by the unhappiness of the affected families and, above all, by the great wish of defeating the destiny on the part of all the human beings"[42]. This assessment, in spite of its hardness, contains, in my opinion, fair elements which indicate to what the research in human molecular genetics in its different areas of develop-ment is in debt, such as the Human Genome Project which was analysed in the previous chapter and the gene therapy which is commented in this one. In spite of this, as I have already pointed out, the somatic gene therapy contains therapeutic potentialities to combat many diseases which are incurable at the moment, which would be absurd to deny. That is why the research in this field and its cautious application in well controlled clinic trials must be accepted.

It does not happen the same with the germinal gene therapy. Although it is not possible to develop a discussion about it due to the extension of this chapter, we must underline that it presents many more problems than the somatic therapy and almost none of its potential advantages. For the people interested in this matter I refer to my essay *A pensamento euxenésico na actualidade*[43], where I carry out a critical analysis of the germinal gene therapy and the so-called improving genetic engineering. I will just summarize very briefly my point of view about this kind of gene therapy.

A great part of the criticism addressed to the germinal gene therapy is focussed on the fact that it produces the permanent change of the hereditary genetic patrimony in the lineage of the individuals who undergone it. Although this is true, it is not a sufficient reason to reject the germinal intervention from the moral point of view, provided that it is has a clear therapeutic purpose. From my point of view, germinal therapy is rejectable because the therapeutic

objectives which pretends to cover can be reached by other means, without the dangers which would accompany the use of this technique. Among these other means we could include the somatic gene therapy which has already been discussed.

Against this last one, the defenders of the germinal therapy usually argue that the therapeutic effects of the somatic therapy cannot be transmitted to the descendants of the treated person, objective which could be reached with the germinal therapy, if this worked properly. But, even in this last case, the selection of embryos obtained by means of *in vitro* fertilization, and the previous preimplantatory diagnosis of those ones, covers practically all the suppositions (except some very odd exceptions) where we should apply the germinal therapy, without the technical difficulties and the iatrogenic risks associated to the use of it. We have to take into account that its application would also make necessary the preimplantatory diagnosis of the embryos (or the ovules in this case), to detect those bearers of the deleterious gene which must be corrected by means of the therapy. It will always be simpler to select the healthy embryos than trying to modify the genes of the embryos which are the bearer of the disease. There are not, then, therapeutic justifications to opt for the germinal therapy, accepting the dangers associated to it, since it does not contribute any supplementary advantage to the possibilities of the existing techniques.

If the aim was to make genetic engineering improving, introducing any new genetic characteristic not present before, like the genetic resistance to any infectious agent (i.e. the HIV), the germinal intervention would of course be the only way to reach it. But in this case, we are no longer in the presence of a therapeutic intervention and, although they are not part of the objectives of this discussion, the ethical and social problems associated to this kind of intervention, which could be labelled as exactly eugenic, in my opinion make applying to it rejectable[44].

CONCLUSION

The somatic gene therapy, started at the beginning of the 90s, closed the last century with great expectations which, during the course of the following years, had been partially disappointed due to the difficulties and problems which impede the achievement of significant advances. Part of this expectations were promoted by the interests of research groups itself, which needed to find sources of financing their clinical trials. These same necessities, in some occasions, lead to carry out protocols of investigation with little guarantee, and some of the adverse results produced were concealed to the organisms responsible of its control. When the death of a person, caused by the treatment he had undergone, was proved concealed, it caused a crisis of confidence in the gene therapy tests.

Despite these problems the somatic gene therapy techniques have been developing and are still a very promising way, although not so imminent as they thought at the beginning, for the struggle against a good number of genetic diseases.

There is a large agreement on the idea that somatic gene therapy does not create ethical problems different from any other new therapeutic treatment in experimental phase. But it is necessary, above all in the light of the negative experiences, that protocols which are put in practice are developed prudently and with a strict control on the part of the scientific and ethical commissions destined to the purpose. Likewise, it is necessary that the economic interests of the private companies with investments in this field do not negatively interfere in what must be a good and safe practice of clinic experimentation.

As far as germinal therapy is concerned, it turns out to be rejectable because its supposed advantages do not compensate the dangers associated to it, especially if there are therapeutic alternatives with the same potential that do not carry the same risks. Only in the perspective of a human improving genetic engineering, which we reject, would have sense the genetic modification of germinal cells.

KEYWORDS Somatic Gene Therapy. Cancer. Human Genetics

ABSTRACT The present chapter is devoted to the analysis of the gene therapy. After a discussion about the reach of its definition, their different modes are decribed and the necessary conditions for its application are examined. Then it is carried out a brief account of the main experiences and tests about gene therapy made a date. The last part of the chapter is devoted to the discussion of the problems which somatic gene therapy presents, some of them derived from the lack of transparency and the no rigorous application of the safety regulations which is necessary to respect in every treatment which has a experimental nature. To finish it is made a short critical assessment of the gene therapy in the germinal line.

NOTES

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17. Theodore FRIEDMANN, Problemas de la terapia génica, *Investigación y Ciencia*, nº 251, August 1997, pp. 44-50.
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35. Alain FISCHER, Límites y esperanzas de la terapia génica, *Eidon*, February / May 2001, nº 6, p. 19.
36. Lydia FEITO GRANDE, *El sueño de lo posible. Bioética y terapia génica*, *op. cit.*, p. 344; Edward M. BERGER and Bernard GERT, Ética de la terapia génica, *Perspectivas bioéticas* 1999, vol. 4 (7-8), pp. 30.
37. Miguel MORENO, *Modelos y presupuestos en la divulgación de los avances en terapias génicas y clonación*, *op. cit.*, p. 11.
38. Juan Ramón LACADENA, *Terapia génica*, *op. cit.*, p. 1.
39. See quotation 35 in the chapter 8.
40. Phenylalanine is one of the essential amino acids and, that is why it must be present in the diet, even in the phenylketonuric people's diet. The suitable diet for them does not lack completely of this amino acid but it must be found in the minimum quantities, indispensable for the formation of the proteins, but low enough to avoid its harmful accumulation.
41. Quoted by Miguel MORENO, *Modelos y presupuestos en la divulgación de los avances en terapias génicas y clonación*, *op. cit.*, p. 15.
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