Gene therapy and inborn metabolic disorders: a feasible alternative

Terapia gênica de distúrbios metabólicos herdados: uma alternativa viável

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In 1992, a gene for low-density lipoprotein (LDL) receptor was introduced into the liver of a patient with familial hypercholesterolemia. It was the beginning of hepatic gene therapy. Ever since then, the field of gene therapy has presented a fast and significant evolution. In 1995, there were already around 200 protocols in 12 different countries, including approximately 1,000 patients. This number has been increasing significantly in the last few years.

The human genome project will probably describe, before long, all human genes and the sequencing of their billions of nucleotides. At least one-third of the project's work has already been concluded. The mapping of genes, an important task that should be concluded within 1 or 2 years, as well as the effective use of the produced knowledge are useful tools that have been increasingly and successfully employed in diagnosing different types of diseases. The implantation of foreign genes into targeted cells in order to treat or cure diseases, however, is still science fiction to many. Yet, this is an out-of-date point of view that should not be taken into consideration by Brazilian pediatricians. Gene therapy is a perfectly feasible therapeutic alternative, which has been increasingly used in different countries and which should be further discussed and understood by professionals in our area. The National Institute of Health (NIH), in 1995, stopped considering gene therapy as a borderline medical science knowledge; so gene therapy started being accepted as an effective weapon in the war against cancer, infections, cardiovascular diseases, and, evidently, inborn errors of metabolism.

Genetically determined diseases can be classified into three main categories: (a) monogenic diseases, inherited according to Mondei's classical principles and caused by one faulty gene; (b) complex genetic diseases, associated with mutation in various genes, including diabetes, hypertension, and most neoplastic diseases; and (c) acquired genetic diseases, associated with the accumulation of genetic alterations along the patient's life, including hepatitis B and C, and neoplasias. In following this classification, gene therapy may be subdivided into: (1) substituting genes in monogenic diseases; (2) amplifying genes in complex genetic diseases; and (3) blocking gene manifestation and/or function and using vaccines for acquired and complex diseases.

In theoretical terms, gene therapy can be easily understood; its practical application, however, is highly complex. During the last decade, studies have demonstrated that the most significant obstacle in gene therapy is not the unleashing[onset?] of toxic effects, but rather the reduced efficacy attained in clinical assays. There is still the need for better gene transferring methods, for more effective vectors, for improvement in animal models in order to test and compare the effectiveness of vectors, and for better delineated clinical protocols. To be sure, Brazil has the potential to become a center of excellence in gene therapy in Latin America.

In conclusion, when discussing gene therapy, it is important to understand that: (a) 5% of

individuals with less than 25 years of age have presented problems with genetic components; (b) 20 to 30% of diseases of children hospitalized in the US are of genetic origin; and (c) 10% of adults present some type of infirmity that is directly influenced by genetic components. The review article by Dr. José Luiz de Godoy, included in this issue of the Jornal de Pediatria, presents one of the most fascinating progresses of medicine in the last few centuries: gene therapy. The author submits pertinent consideration regarding the gene, the vector, and the targeted cell in the context of liver-related inborn errors of metabolism. It is at the end of this editorial that I would like to quote S. Pena & G. Carakushansky: "it is time for molecular pediatrics."

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