ADVANCES IN GENETICS: WHAT ARE THE BENEFITS FOR PATIENTS?

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Summary

What are the benefits of progress in genetics for patients? The answer of the lay will certainly be: “gene therapy and therapeutic cloning”. Our contemporaries, fascinated by these futuristic prospects, tend to ignore the growth of currently available conventional treatments and the impact of symptomatic management on quality of life and life expectancy of patients with genetic diseases. This is due to a problem of information in the oversimplified context presented by the media, in which fashion is more important than reality and the sensational is more important than objective information. Here, we try to honestly establish the inventory of what is already possible. In the light of several examples, we wonder whether replacement of a gene - the identification of which is essential for the understanding of a disease - is truly the universal panacea for the treatment of genetic diseases.
What are the benefits of progress in genetics for patients? If you ask the question to senior high school or university students, the answer will certainly be: “gene therapy and therapeutic cloning”. Our contemporaries, fascinated - and not without reason - by these futuristic prospects, tend to ignore the growth of currently available conventional treatments and the impact of symptomatic management on quality of life and life expectancy of patients with genetic diseases.

This is not due to ingratitude, but to a problem of information in the oversimplified context presented by the media, in which fashion is more important than reality and the sensational is more important than objective information. Let us try to render unto Caesar that which is Caesar’s and honestly establish the inventory of what is already possible. In the light of several examples, let us wonder whether replacement of a gene - the identification of which is essential for the understanding of a disease - is truly the universal panacea for the treatment of genetic diseases.

The first step of rendering unto Caesar that which is Caesar’s is to remember that several genetic diseases were already treated long before the age of molecular genetics. We did not have to wait for cloning of the phenylalanine hydroxylase gene to treat phenylketonuria by a low-protein diet. One would even go so far as to say that molecular genetics has virtually not had any impact on the treatment of this disease. However, since the 1970s, more than 20 million French babies have been tested at birth (without knowing it) and 7,000 of them, detected and treated early, have avoided mental retardation and are now healthy adults with children of their own. The same applies to many other inborn errors of metabolism, in which dietary avoidance of a toxic substrate (such as phytanic acid in Refsum disease, ref. 1) or a dietary supplement has transformed the child’s life span and quality (high-carbohydrate diet in glycogen storage diseases or medium chain triglycerides in fatty acid oxidation disorders, ref. 2). Moreover, the dietary management of metabolic diseases is continuously improving, as illustrated by the example of protein glycosylation deficiency (CDG1b). In this case, understanding of the mechanism of the disease (impaired isomerisation of fructose into mannose) is synonymous with cure for the patient, as a dietary mannose supplement is life-saving (3). The same applies to rare but not exceptional vitamin-independent forms of metabolic diseases such as biotin-responsive carboxylase deficiency (4), pyridoxine-responsive homocystinuria (5), cobalamine-responsive organic acidurias (6), pseudo-Friedreich’s ataxia responding to alpha-tocopherol (7) and riboflavin- (8) or carnitineresponsive lipid myopathies and cardiomyopathies (9). Once again, never a year goes by without the elucidation of the mechanism of a metabolic disease resulting in a new therapeutic approach. A good example is the rare but spectacular forms of mitochondrial diseases curable by ubiquinone (10) and rare forms of mental retardation and autistic syndromes due to a deficiency of creatine synthesis and curable by oral creatine (11). The real challenge at the present time is not to treat so many different diseases by a diet or the addition of cofactors, but rather to identify among all these children those that can be treated, as their lives are going to be changed.

Render unto Caesar that which is Caesar’s also means remembering that it was not our generation but that of our mentors which first treated hereditary kidney disease by kidney transplantation (Alport syndrome, nephronophthisis and polycystic kidney disease), congenital biliary atresia by liver transplantation, heart malformations by heart transplantation and immune deficiencies by bone marrow transplantation. Remember the daring innovations of the first orthopaedic surgeons and intensive care physicians who first operated on the spines of myopathic children. Remember the pioneers of visceral surgery, who treated Hirschsprung’s disease, diaphragmatic hernias, and gastro-oesophageal malformations.

But our generation has also made considerable progress: for example the fascinating results of electrostimulation of the globus pallidum in torsion dystonia due to mutation of the
gene DYT1 (12), Huntington’s chorea and so many other dystonias. These neurosurgeons, not especially familiar with molecular genetics, have certainly done much more for these children than the whole community of geneticists combined! Render unto Caesar that which is Caesar’s is finally remembering that the pharmaceutical industry has transformed our knowledge into safe and effective pharmacological proteins and enzymes: insulin, growth hormone for the treatment of hereditary dwarfism, factor VIII for haemophilia and enzyme therapy for lysosomal storage diseases (Gaucher, Hurler, Fabry, Pompe diseases, ref. 13). No one claims that gene therapy and cell therapy will not, one day, have their place in the range of treatment options. Yet, for the patient and for the doctor faced with the reality of genetic disease today, these treatments are not available and we need to find tricks to hold on until this breakthrough really takes place.

Such tricks include reexpression of a foetal haemoglobin (HbF) gene by hydroxyurea, avoiding the need for transfusion of children with thalassaemia and sickle-cell anaemia (14). Another trick consists of chelating a toxic by means of a drug such as cysteamine for the treatment of cystinosis (15), or blocking a metabolic pathway that leads to accumulation of a toxic substance. For example, blocking the catabolism of tyrosine by NTBC transforms terrible tyrosinaemia type 1 into tyrosinaemia type 2 that is almost benign (16): 90% of affected children are cured! Even more recently, a drug, rapamycin, has been shown to be potentially active in the treatment of Bourneville’s tuberous sclerosis (17), as it replaces the inhibitory effect of tuberin and hamartin proteins in the mTOR pathway, activation of which is responsible for the disease: a promising clinical trial is underway. Another trick was the somewhat incidental discovery that colchicine transforms (although we don’t know why or how) the prognosis of familial Mediterranean fever (18).

Yet another trick consists of enhancing residual enzyme activity by a drug, such as fibrates in fatty acid oxidation disorders (19) or inhibiting a normal function if this function worsens the course of the disease. For example, by inhibiting osteoclastic activity, bisphoshonates limit bone resorption and reduce the consequences of collagen type 1 mutations in osteogenesis imperfecta: the mutation is still there, but multiple fractures and bone pain are considerably reduced (20).

Finally, another trick is to protect a threatened function by a drug, such as short-chain quinones (idebenone) that protect the iron-sulphur centres of the respiratory chain against oxidative stress caused by the absence of frataxin in Friedreich ataxia (21): cardiomyopathy is controlled by idebenone in 85% of children with Friedreich’s ataxia.

We clearly did not wait until the genes and their mutations were identified before starting to treat genetic diseases. Our patients do not suffer from their mutations but from the functional consequences of these mutations. So let’s target the real enemy: accumulating evidences support the view that understanding and properly addressing the mechanism of a genetic disease is tactically more useful to circumvent the problem than replacement of the mutant gene, which is technically very complex. Understanding the exact mechanism of disease: this is the information that we really need in order to devise the new tricks that will change our patients’ lives. Although precise identification of mutations may appear to be useless for treatment it could soon become vitally important for the development of tailormade molecular therapy strategies, as shown by the correction of stop codon CFTR mutations by gentamycin in cystic fibrosis (22).

But, discoveries are not made on command and they take time. We must therefore avoid dogmatism and let ourselves dream, giving free rein to the wildest ideas and paying full attention to incidental observations as they could prove to be very promising and lead to real breakthrough. The treatment of genetic diseases is much too serious to be the subject of passing fads, so let’s not put all of our eggs in one basket.


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