COMMENTARY

Advances in genetics: what are the benefits for patients?

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What are the benefits of progress in genetics for patients? The answer of the lay person 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 oversimplification of information presented by the media, in which fashion is more important than function and the sensational more important than objective information. In this report, I have tried to establish honestly the inventory of what is already possible. In the light of several examples, let us "render under Caesar what is Caesar's" and try to establish 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 it is proposed to be.

The first point to remember is 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. I would even go so far as to say that molecular genetics has had virtually no impact on the treatment of this disease. However, since the 1970s, more than 20 million French infants have been tested at birth for this disease (without knowing it) and 7000 of these, 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 disease¹) or a dietary supplement has transformed the child's expectancy and quality of life (high carbohydrate diet in glycogen storage diseases or medium chain triglycerides in fatty acid oxidation disorders²). 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 dependent forms of metabolic diseases such as biotin responsive carboxylase deficiency,⁴ pyridoxine responsive homocystinuria,⁵ cobalamin responsive organic acidurias,⁶ pseudo-Friedreich's ataxia responding to α -tocopherol⁷ and riboflavin,⁸ or carnitine responsive lipid myopathies and cardiomyopathies.⁹ Not 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 those affected children that can be treated, as their lives are going to be changed.

We also need to remember 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. However, our generation has also made considerable progress; for example, the fascinating results of electrostimulation of the globus pallidum in torsion dystonia caused by mutation of

the *DYT1* gene,¹² and in 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. We must also remember 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 and Pompe syndromes¹³).

No one claims that gene and cell therapy will not, one day, have its place in the range of treatment options. However, for the patient and doctor faced with the reality of genetic disease today, these treatments are not available and we need to find other "tricks" to use until this breakthrough really takes place.

Such tricks include inducing re-expression of the foetal haemoglobin (*HbF*) gene by hydroxyurea, avoiding the need for transfusion of children with thalassaemia and sickle cell anaemia.¹⁴ Another consists of chelating a toxin by means of drugs, 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 the severe tyrosinaemia type 1 into tyrosinaemia type 2, which is almost benign:¹⁶ 90% of affected children are cured. Even more recently, 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 treatment was the somewhat incidental discovery that colchicine transforms (although we do not know why or how) the prognosis of familial Mediterranean fever.¹⁸ Yet another involves 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, bisphosphonates 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, it is possible to use a drug to protect a threatened function, 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's ataxia;²¹ cardiomyopathy is controlled by idebenone in 85% of these children.

We clearly did not wait until genes and their mutations were identified before starting to treat genetic diseases. Our patients do not suffer from their mutations but from their functional consequences. So let us target the real enemy; accumulating evidence supports 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 is the information that we really need in order to devise the new treatments 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 tailor-made molecular therapy strategies, as shown by the correction of stop codon *CFTR* mutations by gentamycin in cystic fibrosis.²²

Nevertheless, 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 us not put all of our eggs in one basket.

J Med Genet 2006;**43**:555–556.
doi: 10.1136/jmg.2005.039966

Received 8 December 2005

Revised version received 8 December 2005

Accepted for publication 8 December 2005

Published Online First 9 December 2005

Competing interests: there are no competing interests.

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