A dose of molecular medicine

Participants at *Nature*'s conference "From DNA to Drugs" in Amsterdam (2–3 December) found that applying molecular biology to medical problems combines daunting challenges with revolutionary possibilities.

Amsterdam. The explanatory power of molecular biology has unexpected ramifications. Introducing his talk on "Protein structure and drug design" last week, Tom Blundell (Birkbeck College, London, and director-general of the Agricultural and Food Research Council) pointed to a residue in the structure of the enzyme porphyrobilinogen deaminase and remarked that a mutation at this spot was responsible for the acute intermittent porphyria that affected King George III of England. That condition led to fits of madness after overeating, the imposition of savage taxes on the American colonies during a royal fit, the American War of Independence (as it is called in Britain) and thus the formation of the United States itself. As an example of molecular pathogenesis, it could hardly be bettered; but as the rest of the meeting showed, the challenge of turning structural insight into effective treatments remains daunting.

Indeed, before it can even begin, it is generally necessary to find the responsible gene. That task will surely become easier as the vast job of charting the human genome draws to a close, and more than 90 per cent of it will soon be physically mapped (Daniel Cohen, Généthon). Even now, though, it is clear that a single clinical entity (such as Friedrich's ataxia) may have more than one cause (Jean-Louis Mandel, Institut de Chemie Biologique, Strasbourg), while different clinical entities (such as multiple endocrine neoplasia type IIa, type IIb and Hirschsprung's disease) can stem from mutations in a single gene, in this case the oncogene *ret* (Bruce Ponder, Cambridge).

Many commoner conditions, including most of the major killers of Western populations, are multifactorial, and pose even more intractable problems. In Europe, a polymorphism in or near the gene for angiotensin converting enzyme appears to be responsible for as many cases of coronary artery disease as smoking (François Cambien, INSERM, Paris). The 4.4 form of apolipoprotein E also seems to be a strong predisposing factor, and has an even more drastic effect on susceptibility to Alzheimer's disease. While these findings are highly significant in themselves, they also surely herald major advances in the understanding of the epidemiology of such conditions.

Elsewhere, there are even fewer clues to follow. A decade after HIV-1 was first isolated, it is still not clear exactly what features of an immune response confer protection against AIDS, so that designing an effective vaccine has proved extremely difficult (Warner Greene, Gladstone Institute, University of California, San Francisco). But a protective response is possible; rhesus monkeys infected with SIV bearing a deletion in the *nef* gene resist subsequent challenge with the native virus, and a small group of San Francisco men have been HIV-positive for more than 12 years without showing any evidence of disease. The hope must be that further study of these cases will eventually allow the design of a vaccine that induces such a response in everybody.

Once the pathogenesis of a condition is clear, the systematic study of therapeutic intervention can begin. But here too, pitfalls abound. The structure of a protein complexed with a potential drug may have to be determined several times before rational design has honed the drug to perfection (Tom Blundell). Similarly, the regions of a mouse monoclonal antibody that determine its complementarity with an antigen are not the only parts that must be retained when it is "humanized", at least if high affinity is to be preserved (Cary Queen, Protein Design Labs, Inc., San Francisco). And the features responsible for efficient targeting of ribozymes, also potential drugs, are only beginning to be understood (John Rossi, Beckman Research Institute, City of Hope, California). Even the seemingly simple oligonucleotide requires multiple chemical modifications before it has the stability and affinity to make a satisfactory reagent (Richard Wagner, Gilead Sciences, Foster City, California).

Nor is it any easier to use reagents expressed by the patient's own cells. Tumour-infiltrating lymphocytes from patients with end-stage cancer can be grown *in vitro* and returned to them, inducing remission in some (Steven Rosenberg, US National Cancer Institute). But success is not common, even when the lymphocytes are made to produce tumour necrosis factor and interleukin 2 to enhance their effectiveness. In other cases, painstaking work with several viral vectors in various tissues has been necessary to obtain satisfactory expression of proteins such as factor IX in mice; even then, success has been difficult to replicate in dogs (Inder Verma, Salk Institute, San Diego). Moreover, even now that mice, at least, can be made to express stable and therapeutically useful levels of a mini-dystrophin gene, questions remain about the safety of the vector and the immunogenicity of the protein (Axel Kahn, Institut Cochin de Génétique Moléculaire, Paris).

On other occasions, of course, immune responses may be turned to good account. Indeed, vaccine design may be transformed by molecular biology before any other branch of medicine. But even here, there are puzzles. Why must recombinant influenza and vaccinia viruses, each containing a different epitope from the major surface protein of the malarial sporozoite, be given to mice in a particular order to elicit an effective immune response (Fidel Zavala, New York University Medical Center)? Why does naked DNA injected into the skin (preferably with a DNA gun) induce an excellent immune response, when the same DNA administered intravenously does very little, even when complexed with liposomes (Harriet Robinson, University of Massachusetts Medical Center)? And why is the canary poxvirus, which cannot even replicate its DNA in mammals, nevertheless highly effective at presenting proteins to the immune system (James Tartaglia, Virogenetics Corporation, Troy, New York).

Clearly, the gulf between the laboratory and the patient remains deep. But already, the first stirrings of a revolution can be seen. Take, for example, the ability to select from a pool of more than 10^7 random peptides the one that can block the growth of *Staphylococcus aureus*, antagonize only one class of enkephalin receptor or lower blood pressure in mice (Richard Houghton, Torrey Pines Institute for Molecular Studies, California). Will not the search for new drugs shortly be changed out of all recognition?

The power of implanted fibroblasts secreting nerve growth factor to reverse cognitive deterioration in aged mice (Fred Gage, University of California, San Diego) also points to an imminent extension of therapeutic competence. Even the hitherto intractable health problems of the developing world are coming under attack, and the possibility of transforming the BCG bacillus into a cheap, safe and effective vaccine against conditions such as leishmaniasis (Barry Bloom, Albert Einstein College of Medicine, New York) raises hopes that they will benefit as much or more than the wealthy West (or North).

None of these developments is yet in clinical use, and none is free from problems. Indeed, it is now clear that many of the hopes and expectations with which the search for 'gene therapy' began were unrealistic. But that in no way invalidates the medical potential of molecular biology. Rather, it is now plain that the dedication of the pioneers in the field has started an advance that will one day be able to improve the existence of everyone on the planet. **Nicholas Short**