Charting the genome

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When historians of the future ponder the twentieth century what will they focus on as its central hallmarks? The holocaust, with its frightening reminder of the fragility of human decency? The rise and fall of communism? The end of the colonial era and the triumphs and trials of the newly independent nations? The women's movement, with its profound effects on one half of our species?"

Thus spoke Sir Gustav Nossal, director of the Walter and Eliza Hall Institute of Medical Research, Melbourne, chairing a recent symposium in Berne that was held to mark the 40th anniversary of the Ciba Foundation. He suggested that all of these issues would be transcended by another—the rise of science and technology as the dominant forces shaping society and dictating the international agenda. He might have added that the subject of the symposium (human genetic information—science, law, and ethics) would assume paramount importance even among the more spectacular peaks of twentieth century science and their social relations. By any standards charting a genome consisting of 4000 million nucleotide building blocks is a massive undertaking; it becomes truly momentous when that genome belongs to the species doing the charting and when the results will inevitably locate genes responsible not only for diseases but also for countless other human traits that may be considered desirable or undesirable.

Ways and means

Charting can, of course, mean one of two things. At a technical level there is a consensus emerging against the option of exhaustive sequencing (compiling an A to Z list of all of the nucleotides). Unlike more "primitive" organisms such as bacteria human cells carry vast amounts of DNA that does not contain any coding information. About 98% of our genome seems to be junk of the sort that in bacteria and other streamlined organisms lacking a separate germline is better termed garbage because it is eliminated in the interests of efficiency. The obvious counterstrategy, as espoused in Berne by Sydney Brenner, director of the Medical Research Council Molecular Genetics Unit in Cambridge, is that of mapping the entire genome and then sequencing only those parts that look interesting.

But how is this work to be organised and apportioned? The current picture is patchy. In the United States the National Institutes

of Health have appointed James Watson, codiscoverer of the DNA double helix, to head a programme of research on the human genome. In Britain Brenner and his team are receiving funds from the Medical Research Council as well as from the Geneva based Louis Jeantet Foundation and the Imperial Cancer Research Fund. At the international level a human genome organisation has been launched to further collaboration and communication. Unesco is hoping to do the same thing; and earlier this year the launch of a European genome programme financed by the European Community was postponed so that work on social and ethical aspects could be incorporated to satisfy the European parliament. Although the meeting in Berne did not clarify this picture, it revealed an urgent desire by the scientists to see vigorous progress. "We need to get this project out of committees and meetings and back into the laboratory where it belongs," said Brenner. "I don't want to be told by some politburo somewhere to do part of chromosome 23."

Genetic intervention should not be attempted

In recent times much discussion of the medical dividends likely to be obtained from mapping the human genome has centred on genetic tinkering to ameliorate diseases attributable to single genes. The same ground was covered in Berne, with general assent to the conclusion of the United States presidential commission's report in 1982 *Splicing Life* that intervention in the human germline should not be attempted. Also, Bob Williamson from St Mary's Hospital, London, reviewed his collaborative work on combining genotyping with in vitro fertilisation to ensure that embryos for implantation do not carry genes for diseases such as cystic fibrosis and Duchenne muscular dystrophy (*Br Med J* 1989;299:22-4).

Williamson emphasised, however, that far more common exploitations were likely to entail environmental and pharmacological intervention after people at high risk of particular diseases had been identified. These include polygenic and multifactorial diseases, formerly considered too complex for genetic analysis to be of any practical value—in some cases too complex even for the analysis to be a practical proposition. One example is coronary heart disease, for which raised serum cholesterol concentration is a major risk factor in non-smokers under 55. In turn, interactions among some 20 genes determine cholesterol concentration. Our

understanding of the genetic basis of hypercholesterolaemia generally had been greatly extended, Williamson argued, as a result of investigations into the more clear cut but comparatively rare condition of defects in low density lipoprotein receptors, in which aggressive measures are required to prevent symptomatic atheroma and atherosclerosis developing by around the age of 40. "In both of these cases," he said, "the most appropriate action is not genetic intervention but strong counselling against smoking and/or the use of drugs to lower blood cholesterol."

Deciding what is beneficial

Bernard Davis of Harvard Medical School expressed a similar shift of focus away from the idea, hyped in the media, of combating hereditary defects by infecting patients with retroviruses as a means of ferrying genes into cells throughout the body. Although the prospect of achieving this effectively and safely seemed remote, a far more promising approach was to introduce genes into a patient's cells cultured in vitro for reintroduction into and colonisation of sites such as the bone marrow. One of the most tempting possibilities was to introduce genetically altered cells to modify immunological actions—that is, to stimulate production of interferon, inhibit autoimmune processes, and increase the responsiveness of the immune system to particular antigens.

One of the most arresting prospects ventilated (but only just) at the Ciba symposium was the imminent mapping of genes responsible for characteristics other than those of medical importance. Clearly, there is now no conviction in often repeated pleas that this would never be done or that the task would be far too complex. Anyone still tempted to use those arguments should ponder Bob Williamson's argument together with one exchange that occurred during the meeting in Berne. Arno Motulsky of the University of Washington School of Medicine had described some research on charting his patients' lipoprotein genes, during which he also came up with data on their colour blindness. Should he give them this information? Motulsky decided against telling (and resolved to ignore these genes in future). "Why didn't you inform your patients?" asked Brenner.

Motulsky answered: "Because I didn't want to worry them."

Brenner retorted: "Don't you think you were obliged to pass on your findings? They might explain a lot of traffic accidents."