Annotation

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Molecular euphoria

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The genetic location of cystic fibrosis is now known and, by the time you read this, probes sufficiently close for clinical use will have been identified. This is a remarkable international collaborative achievement and is justification for those who, undiscouraged, have persisted with family studies in cystic fibrosis and have incidentally broken the deadlock of decades.

Perhaps at this point we should pause and take stock. In a very few years, many of the major Mendelian disorders have been mapped and, in principle, will be accessible to clinically useful gene probing. The list of mapped disease loci is formidable and includes the haemoglobinopathies, familial hypercholesterolaemia, adult polycystic disease of the kidney, haemophilia A and B, Duchenne muscular dystrophy and other important X linked disorders, Huntington's disease, phenylketonuria, α_1 antitrypsin deficiency, and others. We now know that only more hard work is needed to complete the human gene map.

Already, the power of genetic counselling and prenatal diagnosis have been greatly augmented by the use of gene probes and chorionic villus sampling. The principal technical limitations on the use of probes are those associated with genetically uninformative families. The use of highly heterozygous 'minisatellite' and other hypervariable probes will make more families informative, while closely linked flanking probes will increase accuracy of prediction. When there are no surviving patients, it is likely that linkage disequilibrium will allow some prediction by excluding certain haplotypes found with mutants like α_1 antitrypsin deficiency. This may not be very specific for most disorders with reasonably high mutation rates, and useful and precise allele specific probes may not be particularly common, judging by the intralocus molecular heterogeneity of many diseases (for example, thalassaemia and phenyl-

ketonuria). Family studies will still remain important.

The application and exploitation of this new knowledge will include the cloning of genes causing diseases, especially those that are now biochemical mysteries. When sequencing or in vitro gene induction or some other manoeuvre produces the gene product in Duchenne muscular dystrophy or Huntington's disease etc, we will perhaps understand their mechanisms and we may hope that, unlike the haemoglobin disorders, knowledge of pathogenesis will lead to effective treatment. In any case, knowledge of the basic biochemistry of such diseases may partly replace gene probing as the first line of diagnosis and screening, although probably not for early prenatal diagnosis where the exigencies of the situation will require rapid reporting on very small biopsies.

The molecular dissection of disease will do much to elucidate the mechanisms of gene regulation, mutation, and non-disjunction. True primary prevention of genetic disease may then be within our grasp. There is quite simply a vast amount to be done, and much will involve molecular biologists who are not especially interested in the genetics of the families and populations. Those who are will be casting around for new problems. These will be the common diseases of both the western and the developing world.

Clinical geneticists spend most of their time with patients and families with Mendelian or chromosomal disorders and have relatively little contact with common disorders that are not more than casually 'familial'. However, most of us have the comforting belief that the major causes of mortality and morbidity are environmental puppets controlled by (largely invisible) genetic strings and, indeed, many common diseases have genetic 'paradigms'. Thus, the eight or more loci controlling lipoproteins

and LDL receptors may in mutant form produce monogenic disorders like familial hypercholesterolaemia and early coronary artery disease. Rare inherited syndromes like ataxia telangiectasia, multiple polyposis coli, von Hippel-Lindau disease, and 'cancer family' genes predispose to neoplasia. Auto-immune diseases are related to genes in the HLA, IgM- α_1 antitrypsin, IgG kappa and lambda linkage groups. The rapid and profitable growth of interest in dysmorphology includes perhaps a majority of not obviously segregating syndromes together with a large number of rare Mendelian disorders that may share features, like polydactyly or heart malformations, with the commoner sporadic syndromes.

These and others provide possible examples of small numbers of identifiable major genes in 'polygenetic' mixed disease groupings. Do such oligogenic polypathic paradigms actually tell us anything about the aetiology and putative genetic control of common disease? I believe they do and that their molecular study will dissect out homogeneous entities, some of which will be amenable to clinical and preventive pragmatism. One thinks in terms of a small number of major loci having alleles which contribute most of the disease liability, albeit in different combinations, such that none is individually necessary. Disease expression is then dependent on environmental precipitants. This 'ecogenetic' paradigm may be the way forwards in preventive medicine, so that one will identify genetically susceptible cohorts and protect only them from their personal environmental nemesis.

But I am less than sanguine that this will always happen. After all we have known about HLA and

disease for more than a decade and with the exception of good Mendelians like 21-hydroxylase deficiency, complement component deficiencies, and probably haemochromatosis, the link between gene and disease phenotype remains uncertain. We may have to dust off the concept of 'multifactorial determination' and accept that sometimes the coincidence of many normal polymorphic variants at the extreme of the physiological range are responsible for common diseases, especially those in which 'normal' and 'disease' phenotypes overlap. This could be the case in polygenic hyperlipidaemias and coronary heart disease generally, hypertension, dementia, and the major causes of mental ill health.

The challenge is clear. Geneticists and environmentalists must jointly use these marvellous new molecular tools to prize out the secrets of common disease. We must also avoid the sin of excessive parochialism. In the developing world, DNA techniques have already shown how carrier detection and early prenatal diagnosis may be accomplished on some scale for classic and common genetic diseases like thalassaemia, given the will and resources. Geneticists must lead in the public debate on the ethics of 'the new genetics' and this includes the utilisation of resources for the greatest good. Molecular methods will surely help reduce famine by improved contraception and genetic engineering of food plants. Pestilence too will receive a hard knock or two from molecular engineered vaccines. But perhaps it will always be 'too soon' for geneticists to look professionally at the quirks of human behaviour, including those that lead to the third of the tragic trilogy 'Famine, Pestilence, and War'.