BOOK REVIEWS

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Transgenic animals. Eds F Grosveld, G Kollias. (Pp 227; £37.50.) London: Academic Press. 1992.

I'm not sure whether a transgenic experiment has yet found its way into the pages of the *Journal of Medical Genetics*, but if not, it can only be a matter of time. A brief glance through journals such as *Cell* and *Nature* will show that transgenic work is the flavour of the 1990s. But what exactly are transgenic animals, and how could their study be relevant to clinical genetics? This book provides an excellent introduction for anyone wishing to ponder these questions further. The subject matter has been carefully chosen and each of the 11 chapters has been written by expert(s) in the field. The accounts are contemporary, but at the same time comprehensible and, gratifyingly, emphasise general principles rather than the result of last week's experiments from the author's laboratory.

Broadly, a transgenic animal is one whose genome has been artificially modified using recombinant DNA. Such modification can take many forms ranging from, most crudely, insertional mutagenesis causing the random knockabout of endogenous genes; through the introduction of ectopic 'gain of function' genes in self-contained transcription units; to, at the most advanced level, the engineering of specific, targeted alterations by homologous recombination. Transgenic work requires a sophisticated knowledge of normal gene structure and regulation, and some of the general principles are outlined in the first chapter, which sets the scene for the rest of the book. The methodological details are covered in a further four chapters, which successfully avoid the danger of becoming bogged down in minutiae. I particularly enjoyed Rosa Beddington's discussion of the contribution of transgenic work to mouse embryology and development. Special applications include the use of cell markers for lineage analysis; 'gene trap' constructs to document the temporal and tissue specificity of gene expression; 'genetic ablation', a method for inducing the suicide of a chosen cell lineage; and the use of chimeras to determine whether a gene product acts cell autonomously, or can be rescued by neighbouring wild type cells. The chapter on gene targeting contains a useful summary of mouse mutants produced up to the end of 1990; of course, many new ones have appeared more recently.

A further thought provoking chapter is that by Wolf Reik on genomic imprinting. Around 10 to 20% of transgenic strains show signs of imprinting, but no simple pattern emerges: interaction of input DNA, the locus of integration, and the mouse genetic background may all be involved in determining whether 'imprinting' (usually measured as differential methylation) occurs at a particular locus. Incidentally, although methylation is the most widely studied imprinting phenomenon, it seems that there is still no good evidence for or against this being a primary imprinting mechanism.

The final five chapters discuss the specific contribution of transgenic studies to immunology, neurobiology, oncology, gene therapy, and agriculture/biotechnology. The gene therapy section (D Valerio) gives a particularly clear account of retroviral structure and biology, which helps to make sense of the plethora of constructs used to introduce genes into cells. The biotechnology section, written by the AFRC Edinburgh group, includes news of recent success with the production of recombinant human α1-antitrypsin in sheep's milk.

One theme to emerge from early transgenic knockout work is that there may be considerable functional redundancy in the mammalian genome: several research groups have been dismayed to find that homozygous knockout mutants for their favourite 'critical' developmental gene have an entirely normal phenotype. Another is that mice and humans are not the same, as witnessed by the different phenotypes of KIT, HPRT, and RB-1 mutants in the two species. Mouse genetics cannot replace human genetics, but it can help answer experimental questions that cannot be addressed in man. This book constitutes an excellent introduction to that field.

ANDREW WILKIE

The New Genetics of Mental Illness. Eds P McGuffin, R Murray. (Pp 304.) The Mental Health Foundation. Oxford: Butterworth-Heinemann. 1991.

This volume (intriguingly edited by an articulate exponent of the genetic theory and the major contemporary advocate of an environmental interpretation of the aetiology of schizophrenia) reports the proceedings (with some additions) of a conference anticipating major applications of molecular genetics to the understanding of psychiatric illness. The editors declare their intention to present an integrated picture of modern psychiatric genetics. The coverage is wide, and the volume is handsomely produced.

The uninitiated reader seeking a review would do well to start here. For those without familiarity with the principles and promise of molecular strategies, Whatley and Owen provide a readable account, McGuffin gives an outline of the use (and limitations) of quantitative theoretical models, and Clerget-Darpoux of linkage approaches. The logical problems of the latter, and some of the limitations when applied to non-mendelian conditions, are spelled out by J H Edwards. To Lander's conclusion that "if the trait is more complicated than assumed, linkage will not be detected. A negative result to a complete genome search will at least prove that the disease is more complex than had been assumed", Edwards adds that "An assumption needs an assumer". As the findings of the linkage endeavour on the psychoses accumulate and early positive claims fail to find replication, workers in the field might well wish to reflect on Edwards's critque.

The vexed problem of the schizophrenia phenotype is discussed in the context of twin concordance studied by Farmer *et al* with the proposal that the strategy of maximising the MZ/DZ concordance ratio can be used to define the genetic component. The approach is limited, as the authors point out, by the available size of twin samples, but the findings suggest a broad definition including, for example, mood incongruent affective psychoses but not, somewhat surprisingly, paranoid disorder. Gottesman and Bertelsen review more general demographic issues such as whether there has been a secular increase in incidence, concluding that the case is unproven, and the risk to the descendants of affected and non-affected MZ twins, concluding that it is the same. This potentially important conclusion is not strongly supported by a study by Kinglen; in both cases the numbers affected are small.

The interest of the chapter by Gurling *et al* on linkage in schizophrenia is in the conclusions they draw concerning their 1988 claim of linkage to 5q11–13. No subsequent studies have replicated these findings but, at the time of writing this chapter, the authors still argue that the effects of heterogeneity and genetic isolation may yet account for the discrepancies. In the absence of any evidence of linkage in independently studied samples it seems more parsimonious to conclude that this report (like that of the claim of the group of Kidd and colleagues of linkage of affective disorder to chromosome 11) was a false positive finding. The contribution by Jones and Murray stretches the logic of heterogeneity even further. On the one hand they want to argue that schizophrenia is a disorder of development, because abnormality of brain structure (that is ventricular enlargement) is present at the onset, and therefore that genes regulating normal development should be studied as candidates, and on the other hand that the morphological changes are absent (or at least 'less likely') in those cases (the minority it seems) in which schizophrenia can be considered to be truly genetic in origin. Committed protagonists of aetiological heterogeneity, these authors wish to implicate birth complications and maternal exposure to viruses as causative in some cases, whether as additive or independent agents– "thus schizophrenia may result only when an individual inherits several contributory genes or when an individual with the abnormal genotype also suffers fetal adversity". It could be argued that such loose formulations are not susceptible to disproof and therefore in a Popperian sense are not testable hypotheses. If the neurogenetic hypothesis is to make progess a specific prediction concerning the nature of the genetic contribution is required. One such hypothesis, that the relevant genes influence cerebal asymmetry, has been proposed but is not discussed here or elsewhere in the volume.

Life events have been much mooted, particularly in relation to the affective disorders, as precipitants of illness. Bebbington and Kendler and their respective colleagues review compelling findings, that genetic influences are relevant. Some people (maybe 'risk takers') are predisposed by their heredity to encounter more life events. These findings have yet to be taken into account in the more substantial body of publications on the sociological origins of depression.

Other contributions (McGuffin and Sargeant on affective disorders; Treasure and Holland on eating disorders; Rutter on autism) provide useful, critical, and up to date reviews of the relevant publications. Goodman gives a thoughtful analysis of the effect of random factors in development, and of polarising influences (together or apart) between subjects within a family, in determining susceptibility to disease. Concerning the former he writes that "Plomin and Daniels are echoing Gottesman and Shields (1982) and many others when they state that 'Most schizophrenic identical twins do not have an affected co-twin. Because they are genetically identical pairs of individuals, nonshared environment must be the reason for these striking differences within pairs of identical twins'. This is not necessarily so. Another possible cause for behavioural differences between identical twins must be considered; the operation of chance in brain development".

Overall the volume is a useful and well written conspectus of the problems and evidence in the field of psychiatric genetics. It is tempting to hope that the chapter on linkage in psychosis, at least, will soon be overtaken by events, but the experience of the last five years suggests that such optimism is facile. Meantime The New Genetics charts out the promise.

T J CROW

NOTICES

International Symposium on Neurofibromatosis

In collaboration with Professor Jean-Pierre Fryns, University of Leuven, and Professor Claude Stoll, University of Strasbourg, the National Neurofibromatosis Foundation and the International Neurofibromatosis Association are organising an International Symposium on Neurofibromatosis to be held on 11 and 12 September 1993 in Strasbourg, France, as an adjunct meeting to the IVth European Dysmorphology Meeting. For further details contact: Francine Morris, National Neurofibromatosis Foundation, 141 Fifth Avenue, Suite 7-S, New York, NY 10010-7105, USA. Fax 212 529-6094. Tel 212 460-8980.

World Congress on Rett Syndrome

A World Congress on Rett Syndrome, organised by the Belgium Rett Syndrome Association under the gracious patronage of her Majesty the Queen of Belgium, will be held on 8 to 10 October 1993. For further information contact: The Congress Secretary, Peter Vanherck, Lil 26, B-2450 Meerhout, Belgium. Tel 32.14.309494 or 308908, fax 32.14.303157.