Molecular genetics of the mouse

from Grahame Bulfield

WORKERS from two rather different areas came together at a recent conference* in an attempt to relate structure to function in the regulation of mammalian gene expression. One group of workers has been studying the large number of structural and regulatory gene loci controlling enzyme levels that have been discovered in the mouse. A second group, exploiting recent advances in molecular biology, has been looking at the arrangement and sequence of some mammalian structural genes.

The system most completely characterized by genetic analysis in the mouse is that of β -glucuronidase (K. Paigen, Buffalo; see also *A. Rev. Genet.* 13, 417; 1980) and by molecular techniques is the globin system (H. Dahl, National Institute of Medical Research, London). However, the only gene family where both approaches have already converged is the amylase one. Genetic analysis shows that the genes for pancreatic and salivary amylase isoenzymes are tightly linked. The different pancreatic isoenzymes are coded for by up to 20 tandemly repeated structural genes (T. Nielsen, Aarhus) but the sole salivary isoenzyme is the product of a single locus (J.P. Hjorth, Aarhus). These workers have identified over 20 different haplotypes of the complex in wild-caught mice and backcrossed them into the C3H inbred strain. Some of the genetically distinct pancreatic isoenzymes have been characterized by peptide analysis and partial amino acid sequencing (M. Meisler, Ann. Arbor). The A/J inbred strain has one salivary and one pancreatic isoenzyme and a single mRNA species is present in each tissue. The active salivary and pancreatic genes are respectively about 28 and 13 kilobases long and contain at least ten exons. Overall there is a family of about eight amylase-like genes, including one salivary gene, but six of the genes are not expressed in the A/J strain (R. Young, Lausanne) demonstrating a remarkable fit with the genetic evidence. The rat amylase gene has also been cloned as part of an analysis of the structure of the pancreas-specific genes and 12 amylase-like genes have been found (W. Rutter, University of California, San Francisco). The complimentary approaches of the geneticists (in providing a large number of congenic haplotypes) and of the molecular biologists (in providing methods for analysing gene structure) should produce a much better understanding of the regulation of expression of the amylase system.

The workshop provided many reports of new variation available to geneticists, the

characterization of some of the systems and their use in analysing both the regulation of gene activity and of development. Expression of β -glucuronidase is affected by several regulatory loci which map at or near the structural gene and control systemic levels of the enzyme, androgen inducibility and developmental profile (K. Paigen; K. Pfister, Zürich). The different haplotypes of this gene complex should provide valuable analytical material once the gene has been cloned.

Genetic variation in regulatory or tissue-specific mechanisms was reported for many enzyme systems including: alcohol-metabolizing enzymes (R. Holmes, Brisbane), H-2 and related systems (M. Boubelik, Prague; K. Fisher Lindahl, Basel), glycerophosphate dehydrogenase (L. Kozak, Bar Harbor), histidine decarboxylase (S.A.M. Martin, Leicester University), metallothioneins (D.M. Hunt, Queen Mary's College, London), neuraminidase (J. Peters, Harwell) and pyruvate kinase (K.J. Moore, Leicester University). Novel methods of investigating genetic regulation were introduced for teratocarcinomas (W.F. Dove, Madison), by the use of spontaneously occurring trisomics (A. Gropp, Lübeck; R. Fündele, München) and by the flow sorting of mammalian chromatin (L. Bolund, Aarhus). Many of the variants in the enzyme systems listed above have unusual features suggesting that the complexities of genetic regulation will be various and may be difficult to unravel. Further extensive genetic variation, so far little used, was shown to be available in different species (interfertile with laboratory mice) and sub-species of feral mice throughout Eurasia (L. Thaler,

Montpelier; E. Capanna and A. Gropp, Rome/Lübeck; K. Moriawaki, Mishima).

The use of biochemical variants to analyse the nature of one developmental problem — X-chromosome inactivation — was discussed in depth. An electrophoretic variant of G6PDH found in *Mus caroli* has been used to show that, in the germ cells of heterozygous fetuses, one X chromosome is active at the 10th day *post coitum*, whereas both are active between days 11 and 14 *post coitum* during the leptotene to pachytene stage of meiosis (V. Chapman, Buffalo). A 'Catherine-wheel' model has been proposed to incorporate the X-chromosome activation-inactivation cycle in the germ cells with the progressive X-inactivation of extraembryonic and embryonic tissues during fetal development (as demonstrated by gene dosage of X-linked enzymes and X-linked electrophoretic alloenzymes (M. Monk, M. Harper and A. McMahon, University College London). That X-inactivation may itself be under genetic control was shown by three alleles of the *Xce* locus which modify the extent of inactivation on the X chromosome they inhabit (B. Cattanaach, Harwell).

Most of the discussions that took place during the conference were concerned with the validity of the genetical and molecular approaches and how they might compliment one other. Two important points were made: first, the need to concentrate on a few systems and analyse them in detail and second, the need to overcome the geneticists' inability to obtain recombinants between structural and regulatory loci within a tightly linked gene complex. Such recombinants will be essential to relate different DNA sequences to changes in phenotype. □

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Are QSO absorption lines extrinsic?

from Derek Wills

THE observation of quasi-stellar objects (QSOs) in the ultraviolet (UV), made possible by rocket and satellite developments in the past few years, promises to help decide between alternative explanations of some properties of these still puzzling objects. One of the latest developments is that improved measurements of 3C273 in the UV lend support to the hypothesis that the absorption lines in the spectra of this and other QSOs are due to intervening galaxies (or other material) and that they are not intrinsic to the QSOs themselves.

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The first QSO whose redshift was determined is the radio source 3C273, which was observed spectroscopically by M. Schmidt (*Nature* 197, 1040; 1963). Although more than 1,500 QSO redshifts are now known, 3C273 is still the brightest (magnitude 13) and has almost the smallest redshift (0.16). Observations of 3C273 in the UV region are of particular interest because, at this relatively small redshift, it is possible to examine a spectral region that is seen from the ground only in QSOs at much larger redshifts. The result is a direct comparison of physical conditions in objects at quite different cosmological distances and, thus, at different cosmological epochs. Study of the UV

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