BIOMETRICS

Disease Inheritance

from a Correspondent

MULTIFACTORIAL models for the inheritance of liability to disease was the subject of a symposium held in London on February 15 and organized by the British Region of the International Biometric Society.

Some diseases are known to be caused by a single recessive gene. If this gene causes death before adulthood, then the parents of an affected child must both be heterozygous for the gene and hence the risk of the disease for any other child they bear is one in four. Many diseases seem to have a genetic component but not to be inherited in this simple way. Only a proportion of the individuals homozygous for the recessive gene may have the disease and some individuals not homozygous for the recessive gene may have it. The multifactorial model assumes that there are many genetic loci and many environmental factors involved in the causation of the disease.

Professor D. S. Falconer (University of Edinburgh) reviewed the development of the threshold model and his own work on diabetes. In the threshold model, each person has a liability to the disease that can be measured on some continuous scale. The individual succumbs to the disease if his liability exceeds some threshold value. The threshold may depend on sex and age. The liability is inherited in the same way as other continuous characters. The idea of an abrupt threshold may be biologically unacceptable but the threshold model is mathematically equivalent to a more realistic model in which some underlying variable takes different values for different individuals, correlated for relatives, and the probability of having the disease is a sigmoid function of this underlying variable. The parameters of the model are estimated from the incidence of the disease in the general population and the incidence of the disease in relatives of the affected individuals. Making some genetic assumptions, the model can be used to calculate risks for other types of relatives of the affected individuals.

Dr C. Smith (University of Edinburgh) discussed approximate and exact methods for computing risks when information is available for a number of relatives of an individual. Professor Falconer and Dr Smith discussed the evidence for a multifactorial determination of certain diseases. Dr Smith commented on the difficulties of distinguishing, on the basis of data on disease incidence, between models involving a single genetic locus and multifactorial models involving many loci.

Dr C. O. Carter (MRC Clinical Genetics Unit, London) presented evidence, including some concerning sex differences in disease incidence, for the multifactorial determination of some common congenital malformations, such as harelip and cleft palate. He argued that the complex nature of foetal development and the prevalence of genetic polymorphisms support a polygenic model rather than a single gene model with low penetrance. The polygenic model gives a better fit to data on low frequency malformations. For higher frequency malformations the polygenic model is less easy to verify but the single locus model, together with the low fitness of parents, would imply a very high level of mutation.

Professor J. H. Edwards (University of Birmingham) argued that the multifactorial model may be used deductively to calculate recurrence risks but is of no use for the inductive development of more soundly based explanatory models. He saw future progress coming from an increased understanding of the basic but complex genetic determinants of the disease. He stressed, as did the other speakers, the dangers of always interpreting familial correlations as attributable to heredity rather than environment. In the discussion the possibility of virus transmission being a chief cause of familial correlations was mentioned.

The complexities arising from a range of patterns of causation even of a single disease were not discussed in detail. There was very little discussion of possible deficiencies in the data used to estimate disease incidence. The difficulty in discriminating between different models of inheritance has an advantage in a certain robustness of the predictions from any model to the inadequacies of that model. The real questions concern the extent to which empirical data can be extrapolated to predict risks for more distant relatives and the extent to which more complex family data can be used to improve these predictions. When does the extrapolation give better estimates than available empirical data?

Dr Smith mentioned recent work on the use of values of a trait correlated with the underlying variables to improve the prediction of risk. This may increase understanding of the nature of the underlying variable. There can be no argument that statistical models are only a substitute for a more basic understanding. There will be different estimates of how long it will be before statistical models for disease inheritance are no longer necessary.

INSECT HORMONES

Ecdysone Problems

from our Insect Physiology Correspondent

ACCORDING to accepted theory the hormone responsible for initiating growth and moulting in the insect is secreted by the prothoracic glands when activated by the product of neurosecretory cells in the dorsum of the brain. The moulting hormone has been generally identified with the steroid ecdysone originally isolated by Butenandt and Karlson from developing pupae of *Bombyx*. But at present this theory is faced with certain problems. In the first place, the original ecdysone (α-ecdysone) is far less active in many insects than the more polar

A Ribosome's Muscle

ALTHOUGH the 50S and 30S subunits of *Escherichia coli* ribosomes have been reconstructed *in vitro* from appropriate mixtures of ribosomal proteins and RNAs, the function of most ribosomal proteins remains to be elucidated. Two exceptions are the L7 and L12 proteins of the 50S subunit which apparently function in translocation during protein synthesis. These two proteins are also remarkable because they differ in only one respect, the N terminal serine residue of protein L7 is acetylated whereas the N terminal serine of L12 has a free amino-group. In *Nature New Biology* next Wednesday (March 14) Wittman's group, Thammana *et al.*, report data which indicate that each 50S subunit contains at least two and probably three copies of L7 and/or L12.

Estimates of the amounts of L7 and L12 proteins that can be recovered from ribosomes labelled uniformly indicate that each ribosomal subunit has at least one copy of each protein. A quantitative immuno-precipitation procedure also indicates that each 70S ribosome contains approximately three L7/L12 molecules. In short, all the data Thammana *et al.* have obtained indicate that in the ribosomes isolated from bacteria growing at different growth rates the total amount of L7/L12 remains constant—three molecules per ribosome—even though the proportion of acetylated L7 molecules to unacetylated L12 molecules may vary.

Why do ribosomes contain multimeric copies of L7/L12 but only single copies of most other ribosomal proteins? Both L7/L12 have chemical similarities to contractile proteins which usually operate in multimeric assemblies. Thammana *et al.* suggest therefore that "the multiplicity of L7/L12 in the ribosome may reflect a requirement for a replete structure to affect movements of the ribosomal subunits with respect to each other".

©1973 Nature Publishing Group