IV

Quantitative Genetics and the Prediction of Phenotype from Genotype

The translation from genotype to phenotype represents one of the most complex problems in biology. Classic quantitative genetics seeks to predict phenotypic change through single generations by imposing a highly simplified model of genetic determination on data obtained from specific mating designs. Least-squares analysis applied to these data maximizes the fit to an additive model of gene action. Interactions (intra or interlocus) are treated as a residual term. This model works well for short-term prediction, but it tells us nothing about the actual gene action that determines the character of interest. Both Clark and Lynch deal with this problem, but from rather different perspectives. Wu considers the problem of speciation in the context of gene interaction.

Clark (Chapter 11) takes human medical genetics, where the data are more extensive than in any other biological system, as a starting point in his exploration of the prediction of phenotype from genetic data. He makes an obvious but crucial distinction between medical genetics and agricultural applications of quantitative genetics by observing that in medical genetics the problem is to predict an individual phenotype, whereas in agriculture the problem is to predict changes in a population mean value. For the goal of predicting an individual phenotype, Clark lists several fundamental problems associated with the prediction of genetic risk in individuals, and he notes cases in which major mutations have failed to predict a significant proportion of the variance in risk in the population (e.g., *BRCA1* fails to account for the great majority of the risk for breast cancer).

Clark then goes on to ask a very important question: Can we understand the genetic basis of a complex phenotype from analyses of marginal effects abstracted from a system of much higher dimensionality? The motivation for this question is that in genetics we always observe a marginal system abstracted from an unobserved system of much higher genetic

dimensionality. Does it matter if factors not observed in the experimental protocol interact with the factors actually measured? Clark shows by exploring the *NK* model of Stuart Kauffman that it can matter a great deal. Consideration of genotype × environment interaction also involves a complex system where inferences almost always are drawn from a subset of the total range of environmental possibilities. Clark notes that a system characterized by "complex and rich interactions among its components will in general appear to be simpler when viewed at a coarser level of resolution." It is unlikely that marginal analyses will accurately predict the behavior of a complex system with interacting components.

Lynch (Chapter 12) considers recent developments in quantitative genetics and asks whether these will provide a deeper understanding of the nature of adaptive variation and of the limits on rates of adaptive evolution. The development of quantitative trait locus analysis is discussed as a major advance in recent years, although this approach has two major limitations. The first is the inability to detect genes of small effect, and the second is a bias toward false-positives. Lynch asks whether existing quantitative variation is relevant to evolutionary adaptation or whether it is simply the residue of a mutation–selection balance. This question is fundamental to understanding the adaptive limits of population response, a crucial consideration in an era of increasing environmental change.

Wu (Chapter 13) considers the search for general rules in understanding speciation and the genetic nature of species differences. He discusses Haldane's rule and argues that students of speciation have been misled by a misplaced search for generality. He then address the problem of extrapolating from gross genetic measures of species differences to the underlying gene interaction systems that are responsible for reproductive divergence. Finally, he asks whether short-term studies of evolution are adequate guides to the processes of change that span millions of years.

The phenotype–genotype dichotomy is at the core of modern biological research. Evolutionary genetics approaches this complicated terrain from the methodological position of statistical inference. The existing statistical methodology is unlikely to be adequate to this task, thereby limiting our knowledge.