# THE GENETICS OF ELECTROPHORETIC VARIATION

In the April issue of this journal (Genetics **91**: 695–722) there is a paper by V. FINNERTY and G. JOHNSON, "Post-translational modification as a potential explanation of high levels of enzyme polymorphism," which reports that loci other than the structural gene locus for xanthine dehydrogenase may affect the electrophoretic mobility of the enzyme. Unforunately, in an attempt to establish a general significance for this finding, FINNERTY and JOHNSON suggest repeatedly in their paper that post-translational modification may explain a significant amount of the very high variation recently reported in natural populations of Drosophila for loci like xanthine dehydrogenase and esterase. This interpretation, however, is conclusively and definitively contradicted by the known facts.

FINNERTY and JOHNSON report that segregation at the *lxd* locus on chromosome *2* and the *mal* locus on the *X* chromosome in *Drosophila melanogaster* may affect the electrophoretic mobility of the protein coded by the structural gene for xanthine dehydrogenase on chromosome *3*. This finding is reasonable, since these modifier loci have long been known to affect activity of xanthine dehydrogenase.

There are three features of the work of SINGH, LEWONTIN and FELTON (1976) and COYNE (1976) on xanthine dehydrogenase variation in *D. pseudoobscura*, of increasing generality, that completely rule out these modifier loci, or any other modifier loci, as the source of the immense variation so far observed in natural populations.

(1) The *mal* and *lxd* loci cannot be specifically involved. These loci are both on the *X* chromosome in *D. pseudoobscura* and *D. persimilis*, and in our work during the creation of the isogenic lines from wild populations, all wild *X* chromosomes were replaced by the *X* chromosomes from the marker stock. FINNERTY and JOHNSON have attempted to minimize this fact by suggesting that the chromosomal homologies are weak, perhaps under the impression that the evidence for homology rests on some general cytological grounds. But the homologies were established originally on comparative genetic grounds by DONALD (1936) and BEERS (1937), and the recent discovery of many enzyme loci has completely confirmed these homologies.

(2) Irrespective of the location of *mal* and *lxd*, no genetic segregation on any chromosomes except chromosome *2*, which contains the *Xdh* structural gene, can be involved. *All* of the variation found by our group was between lines isogenic for chromosome *2*, and none of it was within these lines. Since only chromosome *2* differs between lines, but is constant within lines, the variation is definitively on that chromosome.

(3) Irrespective of any evidence about genetic segregation, the variation we have observed cannot be the result of any known mode of modification and cer-

tainly not of post-translational modification. The incontrovertible evidence for this statement comes from the fact that in heterozygotes between two electrophoretic variants, the bands retain the same mobility that they show separately in homozygotes. If form A was identical with form A′ at the structural gene locus, but differed because of post-translational modification coded by some other locus, (or cytoplasm for that matter), then in the heterozygote *A/A′*, both proteins would be post-translationally modified. This is not what happens. While we consider our statements and photographs on this issue in SINGH, LEWONTIN and FELTON (1976) and COYNE (1976) to be convincing, FINNERTY and JOHNSON were unsatisfied. In order to leave no doubt on this issue, then, we have made a set of demonstration gels, shown in Figure 1. Isofemale lines on which our previous work was based were crossed to a strain homozygous for a slow allele at the *Xdh* locus, $Xdh^{90}$. Figure 1 shows single heterozygous flies from 36 of these lines, chosen randomly (these gels were run under two different electrophoretic conditions). A great deal of variation is observed among the fast alleles brought

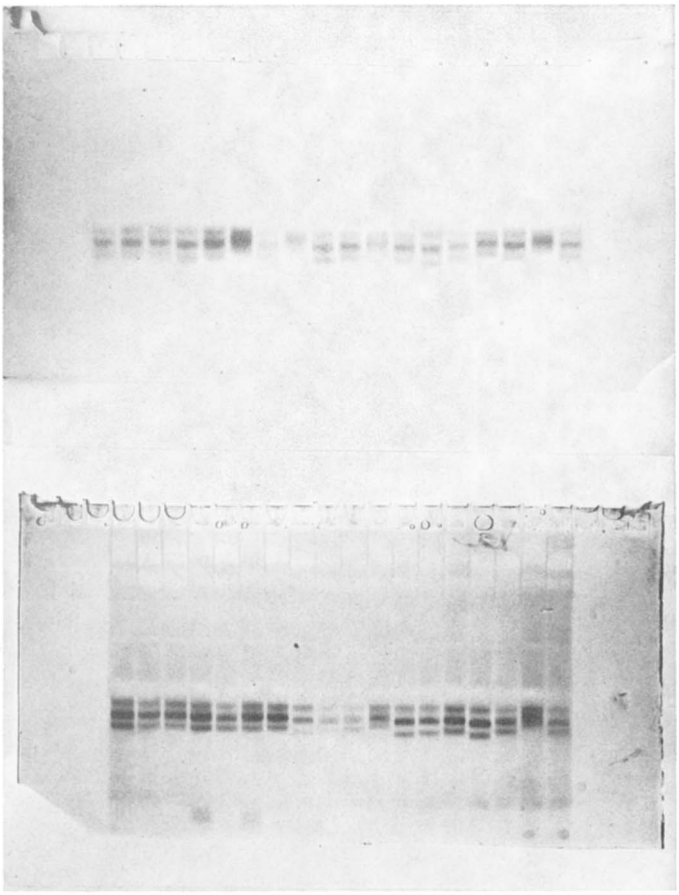

FIGURE 1.—(See text for explanation.)

in from the wild lines; but under all four electrophoretic conditions of SINGH, LEWONTIN and FELTON (1976), the slow allele remains absolutely constant in mobility, the heterodimers falling halfway between. No known form of modifier gene will produce these results and certainly not the post-translational mechanism offered by FINNERTY and JOHNSON. Indeed, to explain these results by other than allelic variation at the structural gene locus would require a linked *cis*-acting modifier, as mentioned in SINGH, LEWONTIN and FELTON (1976).

The same reasoning as given above also applies to the "hidden variation" observed by COYNE, FELTON and LEWONTIN (1978) for esterase-5 in *D. pseudoobscura*. See especially their Figure 1B, showing heterozygotes.

Although the variation so far observed in natural populations cannot be the result of post-translational modification, it is entirely possible that such variation might exist *in addition* to what has so far been discovered. The way to search for such variation would be to hold constant the chromosome carrying the structural gene locus and to search among other chromosomes for variation. This must be done for each chromosome pair in the genome. As it happens, the crosses made for the demonstration gels in Figure 1 accomplish this for the *X* chromosome as a by-product. Each fly in Figure 1 is an $F_1$ male from a cross of a female from an isofemale line with a male from the $Xdh^{90}$ stock. Thus, each fly is hemizygous for a different random *X* chromosome from nature. In all, 52 such crosses were made, 36 being shown in Figure 1. In not a single case was the $Xdh^{90}$ allele affected, so that post-translational modifiers on the *X* chromosome must be rare, if they exist at all. In addition, B. COCHRANE and R. RICHMOND (personal communication) have failed to find among 50 third chromosomes from the wild any occurrence of a modifier of esterase-6 mobility in *D. melanogaster* that had been reported by COCHRANE (1976). Despite these negative results, a further search should be made.

We regret the necessity of correcting the error of FINNERTY and JOHNSON in print, but we have made repeated attempts to communicate the logic of the situation to them, including a photograph from Figure 1. For reasons best known to themselves, they have persisted. There are many real problems of experiment and theory concerning the electrophoretic variation of proteins in natural populations. It would be unfortunate if workers in this field were distracted by a false problem.

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