Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

PARADOX FOUND

False facts are highly injurious to the progress of science, for they often endure long; but false views, if supported by some evidence, do little harm, for everyone takes a salutary pleasure in proving their falseness.

C. Darwin, *The Descent of Man*

IT seems only yesterday that I took my deproteinized bacterial DNAs, worked up in the Caltech Chemistry Building, down to the Delbrück phage laboratory where HARRIETT EPHRUSSI-TAYLOR helped me to assay individual markers by pneumococcal DNA transformation. There I encountered BOB EDGAR and CHARLEY STEINBERG, deep in debate after tabulating data from a gigantic phage cross. Over the summer they were joined by DICK FEYNMAN who, I had learned on my first day at Caltech, was the fun-loving intellectual hero of the student body.

Today, to my surprise, I observe that it was 25 years ago that GENETICS published a pair of papers by EDGAR and STEINBERG, the first also involving FEYNMAN. Each of these three investigators has remained active, EDGAR now working on *Caenorhabditis elegans*, STEINBERG serving as a resident energizer and critic at the Basel Institute of Immunology and FEYNMAN, as followers of the inquiry into the *Challenger* disaster will know, still wearing a Joseph's coat (see FEYNMAN 1985). Meanwhile, the two GENETICS papers that were so novel in 1962 have since been fully woven into the tapestry of molecular genetics.

It is interesting to reexamine these 1962 papers in a 1987 perspective. To some readers of GENETICS a 1962 phage paper no doubt merely signals a part of the transition from Mendelian genetics to DNA sequencing. To others it may seem a relic of a distant past, a time when formal, rigorous model building, free of specific molecular content, was used to divine whether the gene was linear in fine structure and whether recombination involved heteroduplex DNA. These papers, however, played key roles in the rapid advance of modern genetics.

"Mapping experiments with *r* mutants of bacteriophage T4D" (EDGAR *et al.* 1962) supplemented BENZER's (1961) just-published analysis of the *rII* locus, both showing that the locus was internally linear; while BENZER used the method of deletion mapping, EDGAR *et al.* used quantitative two-factor crosses and also neatly demonstrated high negative interference in two-factor crosses. However, the superb complexity and richness of *rII* genetics was to be in part eclipsed by experimental systems having an important additional feature, one required to reveal the relationship between gene structure and polypeptide structure. These systems, *Escherichia coli* tryptophan synthetase, T4 head protein and T4 lysozyme, provided direct access to gene products, a deficiency of *rII* genetics that persists to this day.

"A critical test of a current theory of genetic recombination in bacteriophage" (STEINBERG and EDGAR 1962) reports a paradoxically negative result. The "current theory" under test was based on EDGAR's strong experimental evidence that phage recombinants which have experienced clustered recombination events were the offspring of heterozygotes. If these heterozygous intermediates involved overlap structures (DNA heteroduplexes), then outside markers should have recombined. Instead, clustered recombinants showed classical segregation patterns: double crossovers were parental for outside markers. This paradox, inexorably argued in their paper, shortly succumbed to the discovery that T4 sports two classes of heterozygotes, heteroduplex "hets" and terminal-redundancy "hets" (SÉCHAUD *et al.* 1965; STAHL *et al.* 1965; STREISINGER 1966). Thus the paradox rapidly provoked its resolution.

It is rare to find a classic paper reporting a simple negative result. However, this era of active ferment in molecular genetics offers repeated examples of inoculation by negative result, by footnote and by unpublished observation. The formal possibility of two classes of heterozygotes had been put forward in an appendix to a paper by NOMURA and BENZER (1961), but was brought into focus only by concrete molecular modeling at the hands of STREISINGER and his colleagues. In the "mapping experiments" paper of EDGAR *et al.*, a set of *rII* mutations, *s1*, *s2* and *s3*, was isolated by FEYNMAN as intragenic suppressors of

other *rII* mutations, "to be reported elsewhere." This suppression pattern, analyzed by FEYNMAN using the notion of side-chain interactions at the protein level and never published (see FEYNMAN 1985), was independently discovered and then magnified by the Cambridge group in its germinal analysis of frameshift mutations and the nonoverlapping triplet code (CRICK *et al.* 1961). The Cambridge group also began erroneously, starting with the notion that intragenic suppression reflected base pairing interactions in mRNA (S. BRENNER, personal communication), but soon found their way. The circle was eventually closed by the Cambridge work on tRNA stems (SMITH *et al.* 1970).

At the time these two phage papers appeared, genetics could proceed in a world of its own and with a precision far exceeding that of the molecular analysis of gene and chromosome structure. On the molecular side, however, doubt persisted as to whether T4 contained but a single, uninterrupted duplex DNA molecule, and even as to whether the subunit for semiconservative DNA replication was a single polynucleotide chain rather than a duplex (CAVALIERI and ROSENBERG 1961). The STEINBERG-EDGAR paradox focused attention on these lacunae, which were then filled by hard-won technical progress in the controlled shearing of long DNA molecules (RUBENSTEIN, THOMAS and HERSHEY 1961) and in measuring the mass per unit length of prokaryotic chromosomes (DAVISON *et al.* 1961; CAIRNS 1961, 1962), both of which created a solid molecular springboard for gymnastics such as terminal redundancy [see STREISINGER (1966) for other aspects of these gymnastics].

My musings over old papers and old science bring me, finally, to something for today. At the end of my walk to the phage laboratory, JEAN WEIGLE shared an enthusiasm from a letter from AL HERSHEY on the latter's continual efforts to determine the structure of phage DNA molecules: "There's nothing like technical progress! Ideas come and go, but technical progress cannot be taken away."

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