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**Fincham J R S.** *Genetic complementation.* New York: Benjamin, 1966. 143 p.
[John Innes Institute, Norwich, Norfolk, England]

This book had its origin in the paradoxical ability of certain pairs of mutants, mapping at the same locus or at least very closely linked loci and lacking the same enzyme, to complement one another either in diploids or in heterokaryons to produce enzyme activity. At first sight this seemed to be in contradiction to the one gene-one polypeptide chain hypothesis. Observations of this kind were explained as due to the formation of heterooligomers composed of different, mutually supportive mutant derivatives of the same polypeptide. The book also explored the question of complementation maps and their possible significance. The opportunity was taken of reviewing the general problem of the roles of recombinational and complementation analysis in defining genes and their sometimes complex functions. [The *SCI*® indicates that this book has been cited in over 220 publications.]

## Defining the Gene

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In the classical genetics of the 1930s and the 1940s, the gene was supposed to be indivisible by recombination; when mutants in the same gene (i.e., alleles) were crossed together, they were expected never to yield nonmutant progeny. The gene was also regarded as a unit of function, so allelic mutants were not expected to be able to complement each other's deficiencies to produce a nonmutant phenotype when present together in diploid or heterokaryotic cells.

In the 1950s it became clear that the functional gene (Seymour Benzer's *cistron*) was demonstrably highly subdivisible in any organism where large numbers of progeny could be screened. The gene as a unit of function remained; the function was in general thought to be specification of the structure of a particular polypeptide. Mutations in the same gene were supposed to affect the same polypeptide and never to complement one another.

It was therefore disconcerting when, beginning around 1958, numerous examples were described in various microorganisms of certain pairs of mutants, defective in the same enzyme, complementating one another to form enzyme activity.[1] Complementation relationships within allelic series could be represented by complementation maps in which mutants were represented by linear segments, with only the noncomplementary pairs overlapping. Some of these maps became quite complex, with the segments forming branches, circles, and circles with linear appendages.

The book summarized the evidence that allelic complementation was due to interactions between different defective polypeptide chains within dimeric or oligomeric proteins. Although we now know that this is not the only explanation, in the enzyme that I had worked on, NADP-specific glutamate dehydrogenase of the fungus *Neurospora* (now known to be a hexamer exhibiting allosteric cooperativity among the monomers), Alan Coddington and I[2] were able to show that *in vitro* complementation between mutant extracts was associated with hybrid oligomer formation.

In 1963 (I think it was at the Cold Spring Harbor Symposium of that year) Bernard Davis, who at that time was the general editor of a new series of biological monographs to be published by W.A. Benjamin of New York, asked me whether I would like to write a book on genetic complementation. I readily agreed, since I thought that the time was ripe for a review not only of complementation between enzyme-deficient mutants of microorganisms, but also of the whole question of how one should define the gene in such classical genetic species as *Drosophila* as well as in microorganisms. I also wanted to discuss the meaning of complementation maps, so far as there was any (I finally concluded that they would remain uninterpretable so long as the three-dimensional structures of the proteins remained unknown).

Davis thought that the first draft was a little short for a monograph, and one of my American friends commented that the book had set a new record for dollars per page. I can understand, however, why it attracted a lot of citations. Authors of the numerous papers, appearing during the decade following 1968, that featured allelic complementation wanted a single reference that would spare them from further library work. Now the novelty has worn off and the citations have largely died away.

There are a number of possible mechanisms through which allelic complementation can occur through interactions within hybrid enzymes: conformational constraints within oligomers (the mechanism favoured in the book); reconstitution of monomers from polypeptide fragments (reviewed in reference 3); and active sites shared between monomers in an oligomer.[4] Allelic complementation is now a problem for the protein chemists,[4] rather than the challenge to gene theory that it once was.

1. **Fincham J R S & Pateman J A.** Formation of an active enzyme through complementary action of mutant alleles in a heterocaryon. *Nature* 179:741-2, 1957. (Cited 55 times.)
2. **Coddington A & Fincham J R S.** Proof of hybrid enzyme formation in a case of inter-allelic complementation in *Neurospora crassa*. *J. Mol. Biol.* 12:152-61, 1965. (Cited 30 times.)
3. **Fincham J R S.** Allelic complementation reconsidered. *Carlsberg Res. Commun.* 42:421-30, 1977. (Cited 15 times.)
4. **Robey E A & Schachman H K.** Regeneration of an active enzyme by formation of hybrids from inactive derivatives: implications for active sites shared between polypeptide chains of aspartate transcarbamoylase. *Proc. Nat. Acad. Sci. USA* 82:361-5, 1985. (Cited 10 times.)




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