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1.

Genetic Recombination: A Brief Overview

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I. What Is Genetic Recombination?

> These cases of novelties resulting through a re-combination of the factors brought in by the original pure types are striking because it is not at first sight evident how the novelty has been produced. Generally speaking, however, the re-combinations form in F_2 a series of types many of which are obviously new combinations of features which could be recognized on inspection as present in the pure parents.
>
> W. Bateson (1909)

Today there are two distinct but related meanings of the term *recombination* in common usage by geneticists. In the quote above, Bateson introduced the term "re-combination" as he was summarizing the effects of independent segregation of several differing parental traits of sweet peas into descendants which showed any of a number of possible combinations of traits from the parents. This process of independent

segregation of certain traits, termed "Mendelian segregation" in salute to the man who first discovered it, we now know to be due to reshuffling of chromosomes during meiosis, when from each pair of chromosomes normally present in cells (one of each pair having come from each parent) only one is selected (usually at random) in the formation of new gametes for the next sexual union.

The second and most notable aspect of "re-combination" which Bateson observed was that occasionally two parental traits did *not* reassort themselves randomly into offspring, but would tend to be inherited in pairs. In Bateson's (1909) example from his work with Punnett on sweet peas:

> The result of extensive counting shows than an approximation to the observed numbers would be produced by a gametic system of such a kind that the combinations of long pollen with blue factor, and round pollen with no blue factor occur seven times as often as the other possible combination. We speak of this phenomenon as *Gametic Coupling.*

Here, Bateson used the term *gametic coupling* to describe the concept which we now generally call *linkage,* i.e., the *non*random association of certain genetic traits from each parent into descendents. Furthermore, Bateson was describing the crucial new aspect of this linkage (coupling) phenomenon, namely, that the linkage was *not 100% but occasionally changed,* i.e., a sort of second-order "re-combination" process that can (sometimes very rarely) rearrange combinations of genetic traits that are normally linked. It is now well known that the phenomenon of linkage results from the close proximity of the genetic determinants (genes) for two linked traits on the same chromosome, so that during meiosis the genes for the particular forms (alleles) of these traits usually segregate together into the resulting daughter chromosomes in gametes. The concept of linkage is suggested in Fig. 1, which shows the set of chromosomes (karyotype) from a cell of a human individual. On chromosome 7 the positions of the locus involved in cystic fibrosis (CF) and the gene for paroxonase (PON) are indicated. These two loci are closely linked (Eiberg *et al.,* 1985; Wainwright *et al.,* 1985) and the corresponding configurations (alleles) of a given individual are usually (90%) inherited together. In contrast to this, a locus such as the gene for insulin on chromosome 11 is segregated into progeny randomly with respect to the ones on chromosome 7, i.e., the insulin gene is unlinked to CF and PON. Further, the occasional separation of a pair of linked alleles such as CF and PON is now well-known to occur by a breakage and rejoining between the homologous chromosomes (the matching pair derived from the two parents—i.e., the two number 7 chromosomes, in this case) in the region between the two genes, such that in the next generation (or some

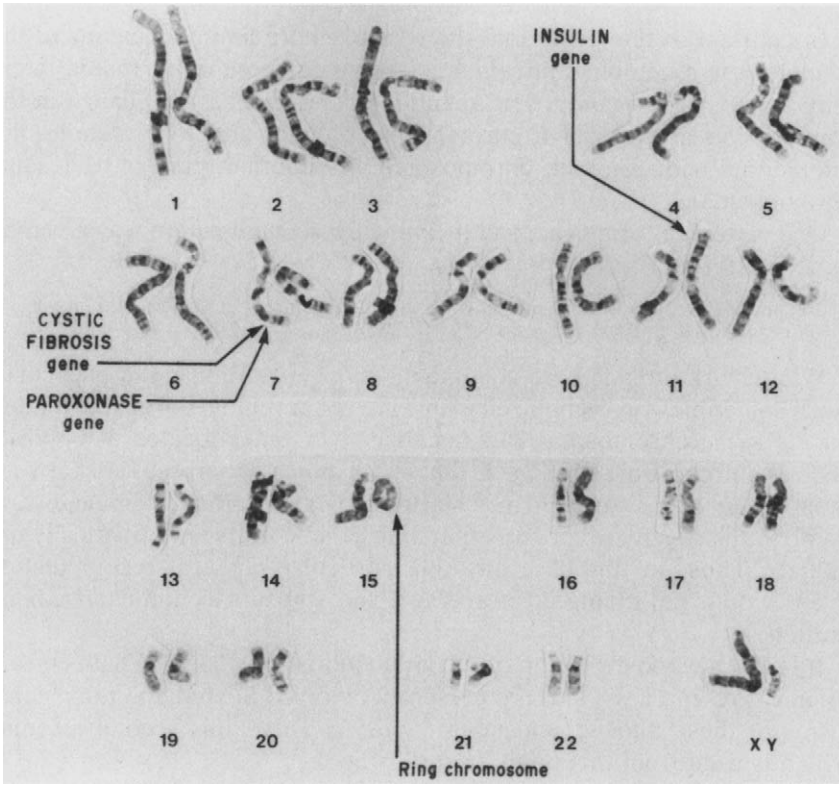


Fig. 1. Human karyotype from an individual with a ring chromosome 15. The genes for cystic fibrosis (CF) and for paroxonase (PON) are genetically linked on chromosome 7, and they are unlinked to the insulin gene on chromosome 11. (From U. Francke and J. Cowan, personal communication.)

succeeding one) a new combination of traits can be observed. This *crossing over,* as it is known, thus corresponds to a molecular rearrangement.

The two different aspects of recombination mentioned above, i.e., independent (Mendelian) chromosome segregation, and changes in linkage (crossing over), are combined collectively to mean *genetic recombination* as the term is currently used by many geneticists of higher organisms, for example, those studying human genetic linkage (Ott, 1985; Suzuki *et al.,* 1986). This definition of recombination was the one intended, for example, by Lederberg (1955):

> Genetic recombination is taken to include any biological mechanism for the reassortment within one cell lineage of determinants from distinct sources.

In contrast to this definition, the second, more limited meaning of the term genetic recombination which is also in common usage today, refers only to the second component mentioned above, i.e., the change in the combination of parts of a chromosome brought about by a molecular interaction with another chromosome (or another part of the same chromosome).

One statement of this second meaning for recombination was given by A. J. Clark (1971):

> Recombination: any of a set of pathways in which elements of nucleic acid interact with a resultant change of linkage of genes or parts of genes.

What Clark intends here is a change in *physical* linkage in particular, since sometimes two genetic elements are so far removed from each other on the *same* chromosome (for instance, two genes located at opposite ends of chromosome 1 in Fig. 1) that many molecular crossovers between them often occur at each meiosis, and they, in effect, segregate randomly into progeny (their corresponding genetic traits are statistically unlinked). Thus, in this case any one particular physical recombination event would not change, on average, the statistically unlinked configuration.

It is this second definition of recombination (i.e., Clark's) that is meant by many researchers who are presently involved in studying the mechanisms of these nucleic acid interactions, and it is this second meaning which is used from this point on in this book.

II. What Are the Major Types of Recombination?

As can be clearly seen from the various chapters which follow, recombinational phenomena are by no means restricted to the crossing over between pairs of homologous chromosomes as in the examples mentioned above. As a result of much elegant and laborious work, a number of distinctly different types of events which involve chromosomal interactions have been observed, and in some cases a great deal is now known of their characteristics. Most fundamentally, these various types of recombination differ in the relationships of the series of four types of nitrogenous bases [adenine (A), cytosine (C), guanine (G), and thymine (T)] in the nucleic acid chains undergoing recombination.

A. Homologous

If the two parental molecules are extremely similar, i.e., have almost the same sequence of bases for many hundreds of bases, recombination

between them at equivalent sites along their base sequence is called *homologous*. Crossover events can occur almost randomly between various corresponding homologous sites along the length of homology. Several topological configurations of this are depicted in Fig. 2, lines A–E. This type of recombination has also been termed "general," "normal," "equal," "chromosomal," "nonspecific," and a number of other terms (reviewed in Low and Porter, 1978). Chapters 2 through 7, 10, and 12 in this volume deal almost entirely with homologous recombination.

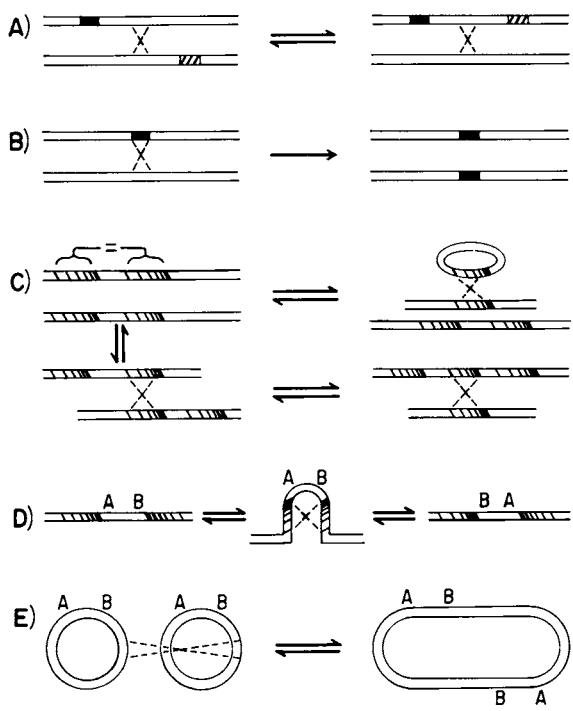
B. Site-Specific

The second major recombination classification, *site-specific*, refers as the name implies, to recombination which has evolved to occur between two very limited and specialized sites. The hallmark of site-specific recombination is that all of the nucleotides in the two parental recombining sites are conserved in a simple reciprocal recombination event. This site-specific type of recombination has also been called "specific," "special," "localized," and other names (Low and Porter, 1978). In chapters 8, 9, and 11 of this volume are described a number of important different site-specific recombination systems, and Fig. 2, lines F–G, illustrates possible topological configurations. Also in Fig. 2 (line H) is depicted a type of recombination between near repeats of various genetic elements, such as in the genes for immunoglobulins (see Chapter 11 of this volume). Though these recombination events usually occur at well-localized regions, the precise position of the exchanges is not always constant, may vary over a range of 20 bases or more, and may involve small additions or deletions (Chapter 11 in this volume Alt and Yancopoulos, 1987). This type of recombination system is thus "quasi-site-specific."

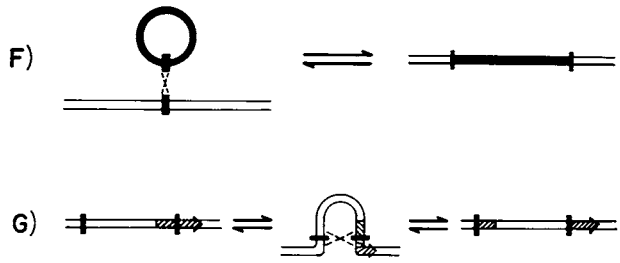
C. Transpositional

A third major class of recombination events also involves specialized sites for recombination, but differs markedly from site-specific recombination. This third class, called *transpositional* recombination, involves the interaction of the two ends of special chromosomal sequences, called *transposable elements*, with a third, more or less random, site on the same or another chromosome. This results in a new position in the genome for the transposable element. Thus, this process involves two specific sites (the ends of the transposon) and a third nonspecific site (the target). Fig. 2, lines I–L, depicts some of the rearrangements that transposition can produce. In chapter 8 of this volume, transposition is discussed in considerable detail.

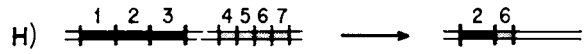
HOMOLOGOUS



SITE-SPECIFIC



QUASI-SITE-SPECIFIC



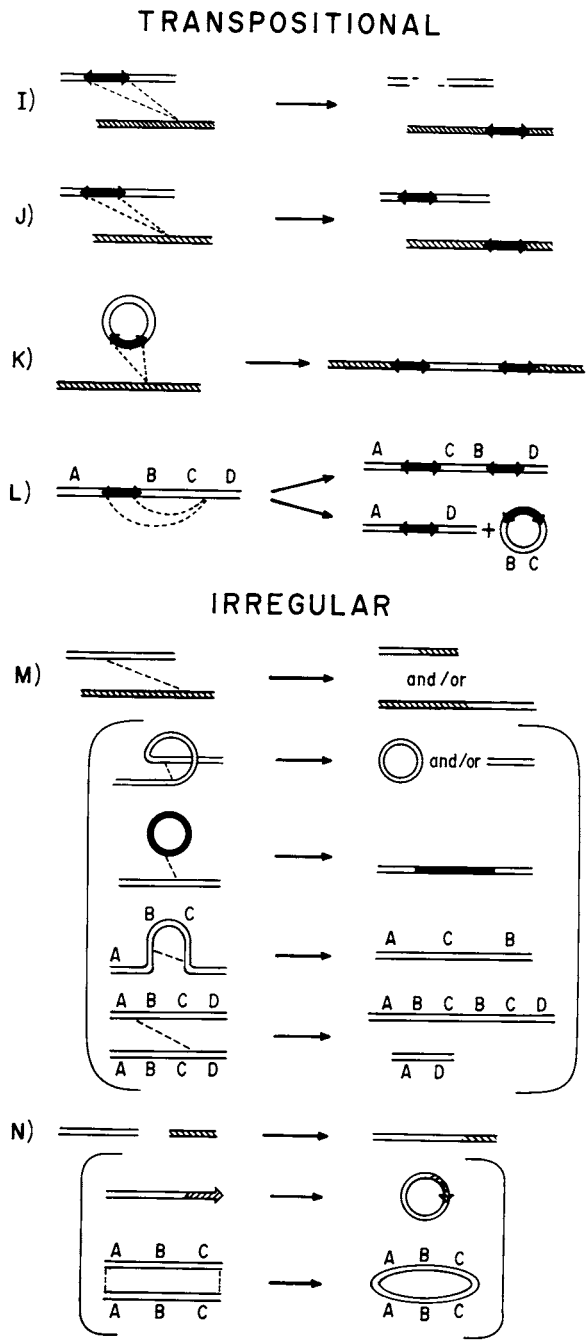


Fig. 2. The four panels depict some of the most common examples of the four major types of recombination: homologous, site-specific, transpositional, and irregular, respectively. The figure indicates the topological configurations of the various chromosomes and the sources of the respective parental genetic information, and is not intended to imply any particular mechanism.

D. Irregular

In rare instances, rearrangements of DNA molecules have been observed to result from an apparent end-to-end fusion process or else a chromosomal crossover which does not appear to involve extensive homology or site-specificity. These types of recombination are indicated as *irregular* in Fig. 2, lines M–N to distinguish them from the former types. A probable example of this type of event is indicated in Fig. 1, which shows an abnormal ring chromosome in which the two ends of chromosome 15 have been joined. The terms "illegitimate," "nonhomologous," and others (Low and Porter, 1978) have also been used to describe these irregular events. However, the term "illegitimate" has been used in different ways at various times (sometimes to include events which we now call site-specific or transpositional), so that its present usefulness is diminished.

Examples of irregular recombination events include apparent end-to-end fusion events in bacteria (Guyer *et al.*, 1977; Horowitz and Deonier, 1985); recombination involving an origin of replication (Kilbane and Malamy, 1980; Michel and Ehrlich, 1986); nonrandom crossovers involving extremely small (if any) regions of homology (e.g., 5–10 base pairs) (King *et al.*, 1982d; Linn *et al.*, 1979; Mertz and Berg, 1974; Nakano *et al.*, 1984; Schmid and Roth, 1983); end-joining of DNA transfected into animal cells (Roth and Wilson, 1985, 1986); and nonhomologous joining of phage λ and plasmid pBR322 (Ikeda, 1986).

In general, irregular recombination can be imagined as a grab bag of processes by which nonhomologous elements are, very infrequently, broken and/or joined in reactions carried out by functions whose main roles are not recombination, but instead some other aspect of DNA metabolism (for example, by enzymes such as polymerases, topoisomerases, ligases, and others normally involved in chromosome replication). This subject has recently been nicely reviewed by Anderson (1987).

III. How is Recombination Detected?

The most readily observable result of recombination, i.e., a change in linkage of detectable genetic markers, is implicit in the definition above, and is recognized, for example, by examining the progeny of a mating between differing individuals to see if pairs of traits that are normally co-inherited (implying physical linkage of the corresponding genetic determinants on the chromosome) are occasionally no longer inherited together. This inference of a change in arrangement of chromosomal

elements (genotype) based on an observed set of physiological traits (phenotype) is the basis for measurements of recombination for the majority of *in vivo* studies in this field. Another approach already alluded to earlier is the cytological examination of chromosomes which allows at least a crude method for detecting chromosomal rearrangements such as the ring chromosome seen in Fig. 1.

More direct physical detection of recombination is also crucial in recombination analysis. Generally, the DNA strands of chromosomes of one parent in a cross may naturally differ in size or density from those of the other parent and those of recombinants, or may be labeled differently–for example, by the incorporation of radioactive atoms, or heavy atoms, or atoms which stain differently when prepared for microscopic examination. The seminal experiments of Taylor (1958), Meselson and Weigle (1961), Wolff and Perry (1974) and Tease and Jones (1978) using these approaches laid the groundwork for an understanding of recombination (at least in many systems) in terms of the breakage and rejoining of DNA molecules (Radding, 1982).

Another type of physical approach, which is now finding extensive use in analysis of recombination products, is that of restriction site analysis, and in some cases, DNA sequencing. Since restriction sites are diagnostic for the presence or absence of many different short sequences of bases, they are finding wide use in studying recombination throughout the evolutionary spectrum (see, for example, Liskay and Stachelek, 1983).

IV. How Often Does Recombination Occur, and How Long Does it Take?

Recombination systems show extreme diversity in terms of recombination frequency and kinetics. Homologous recombination frequency depends not only on the particular organism, but also on the chromosomal position and separation of the genetic markers under study. As a first approximation, homologous recombination frequencies tend to be higher for greater chromosomal separation between markers (however, see the following sections). The separation corresponding to a 1% chance of a crossover per meiosis (known as 1 centimorgan, or cM, after the originator, T. H. Morgan, of the concept of physical crossovers) is on average 10^6 base pairs for the human genome, whose haploid size is approximately 3×10^9 base pairs. This is in contrast to *E. coli* conjugation, where one cM corresponds to approximately 2000 base pairs—i.e., about 500 times more frequent per unit length. However, recombina-

tion probabilities along the human genome are by no means constant, and hot spots exist as well as a generally higher recombination rate near the ends of chromosomes, particularly in males (Kidd, 1987). The chance of homologous recombination occurring *somewhere* in the human genome per meiosis is essentially 100%, in fact 30 or more events are usually distributed somewhat randomly among the chromosomes. (Recombination may actually be an essential part of meiosis.) Likewise, conjunction in *E. coli* almost always leads to at least one crossover event for each cell that receives some homologous DNA from an Hfr donor cell (reviewed in Low, 1987).

The kinetics of recombination also vary from system to system. In *E. coli,* estimates have been made of the time for homologous recombination to occur, such as in the system illustrated in Fig. 3. Though it appears that at least 35 min or more are needed for recombination products to form, it is not clear how much of this time is actually involved in reactions which cut, transfer, and rejoin DNA strands. An analogous experiment in γ-irradiated *Ustilago* suggested that recombination in that system may take 4 to $4\frac{1}{2}$ hours to be completed, following irradiation (Holliday, 1971).

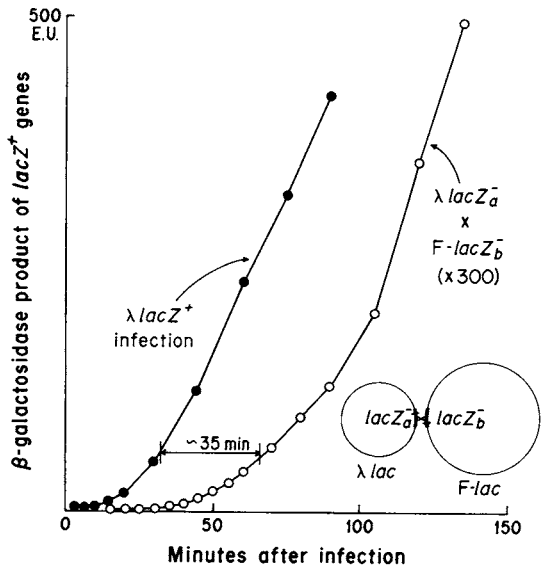


Fig. 3. Kinetics of enzyme production from recombined genes in *E. coli.* The difference in time of appearance of active $lacZ^+$ gene product formed after a $lacZ^-_a \times lacZ^-_b$ cross, compared to a parallel experiment where no recombination is necessary (λ $lacZ^+$ infection) gives an indication of the maximum amount of time (~35 min) required for the recombination steps. (From Porter *et al.*, 1979; Cold Spring Harbor Symposium of Quantitative Biology, 1979.)

Other types of recombination also show a vast dependence of frequency on system. The site-specific integration system of certain phages can be more than 50% efficient per infected cell. In contrast to this, certain irregular events may occur at less than 10^{-8} per cell per generation, and transposition frequencies tend to be in the range of 10^{-4}–10^{-8} per generation.

V. What Length of DNA Can Be Involved in a Recombination Event, and How Much is Necessary?

In an approach to the question of the minimum amount of DNA involved in homologous recombination, Singer *et al.* (1982) obtained results such as those shown in Fig. 4. It can be seen that if less than 50 base pairs of homology exist between parents, very little recombination occurs. It is also clear that increased homology in this system results in increased recombination frequencies. The implications of this 50-base-pair-lower limit are not clear yet, but this sharp drop-off in frequency is apparently different in different systems–e.g., ~70 bases in a case of *E. coli* plasmid–phage recombination (Watt *et al.*, 1985), and ~150 bases in a case of mammalian plasmid recombination (Rubnitz and Subramani, 1984). Nevertheless, if extended homology exists between the parental molecules, recombination can be detected between two markers that are

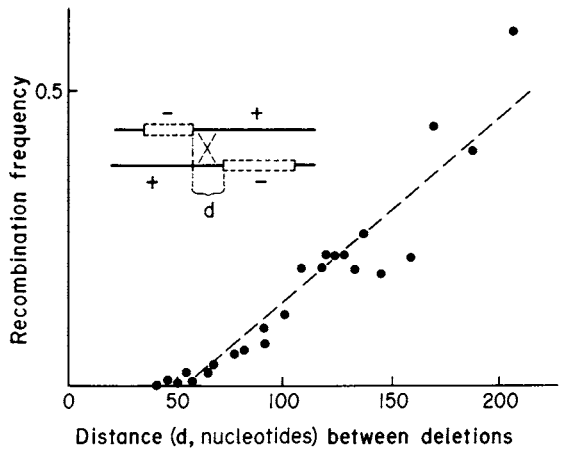


Fig. 4. Dependence of recombination frequency on length of homology for rII mutants of bacteriophage T4. For lengths of homology less than 50 base pairs long, very little recombination is observed. (From Singer *et al.*, 1982.)

as little as one base pair apart (Yanofsky, 1963; Coulondre and Miller, 1977). When the multiple neighboring recombinational exchanges of an event are considered, stretches of DNA as long as 1 to 4 kilobases have been implicated (Ahn and Livingston, 1986; Huisman and Fox, 1986). Detailed descriptions of two such systems are given in chapters 2 and 3 of this volume.

VI. What Indicates That Recombination Is Not "Simple"?

If homologous recombination were a relatively simple process, one might expect that the further apart two genetic markers lie on a chromosome, the greater the chance that they will recombine. Although this is *approximately* true for moderate separations in certain systems (for

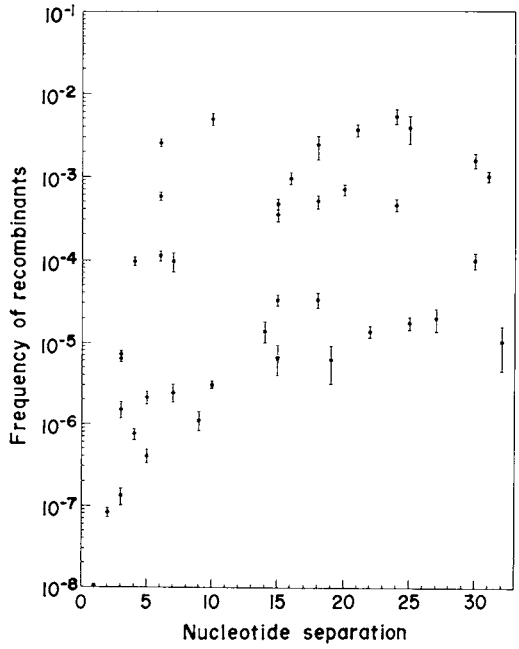


Fig. 5. An example of very large marker-specific effects in F′-chromosome recombination in *E. coli*. Each point shows the recombination frequency for a pair of base substitution mutations in the *lacI* gene, with the abscissa showing the nucleotide separation of the two mutations. (From Coulondre and Miller, 1977.)

example, Fig. 4), great variation from this trend is often true particularly if the markers are very close together. An example of this is shown in Fig. 5 for *E. coli,* and examples are well known in other organisms such as yeast (Golin and Esposito, 1984; Moore and Sherman, 1974) and in humans (Chakravarti *et al.*, 1984). These marker-specific effects on recombination imply considerable subtleties in mechanism, and part of this question is discussed in chapter 4 of this volume.

A further manifestation of complexity in homologous recombination is indicated by the apparent lack of independence of certain closely spaced exchanges induced by recombination—i.e., a phenomenon known as *interference*. When "double" recombination events occur more frequently than expected, based on the probability of each single event, the interference is *negative,* as for example indicated in Fig. 6 for the correlation of close crossovers in conjugation.

A complexity which is easily seen in certain eukaryotic systems is the

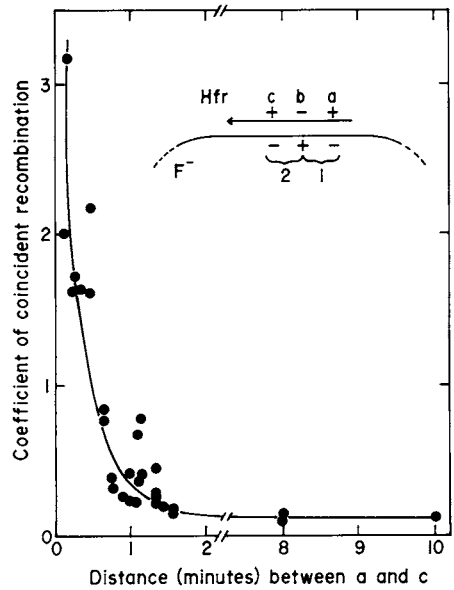


Fig. 6. An example of very large negative interference effects for "double" recombination events very close to each other in Hfr × F⁻ crosses in *E. coli*. The unit of 1 min on the *E. coli* chromosome corresponds to approximately 45 kb of DNA (reviewed in Low, 1987). The plotted values of coefficient of coincident recombination represent the frequencies of recombination in region 2 (between markers b and c) per unit length of chromosome, among recombinants selected for recombination in region 1 (between markers a and b). (From Mahajan, 1971.)

occasional occurrence of nonreciprocal homologous recombination events—i.e., the production of sets of progeny in which one or more copies of one input parental trait is lost ("converted") and instead appears in the form of the other parental trait (depicted in Fig. 2, line B) Chapter 2 of this volume describes such a system in detail.

VII. How Is Recombination Important for Cellular Behavior?

In this section, a few approaches to further reading are suggested for a number of involvements of recombination in fundamental physiological processes.

A. Recombination to Control Genes

At least two general mechanisms exist for the involvement of recombination in genetic control. In certain bacteria and bacteriophage, reversible "genetic switches" enable the organism to switch certain genes on or off, or change the sequence of a gene and thus the sequence of its protein product. These often involve structures on the surface of cells or phage, and presumably have evolved to provide more variety in its interface with its environment (host range for infection, antigen structure, and others). Some of these systems have been found to involve site-specific recombination and examples are discussed in Chapter 8 of this volume, and in Haas and Meyer (1986).

Another type of recombination system more related to homologous recombination (gene conversion in particular) is involved in certain other control systems such as mating type switching in yeast (see Chapter 10 in this volume) and antigenic variation in African trypanosomes. This complex and interesting system is reviewed by Buck and Eisen (1985), Borst and Cross (1982), Borst and Greaves (1987), Donelson and Rice-Ficht (1985), and Pays *et al.* (1985).

B. Recombination, Replication, and Repair

It has been clear for some time, beginning with pioneering recombination-deficient mutant analyses of Clark, Howard-Flanders, and others, that some functions which are needed for recombination are also involved in the repair of DNA damage. The roles of some of the best-studied enzymes of this type, from *Escherichia coli* K-12, are discussed in some detail in Chapters 5, 6, 7, and 12 in this volume.

An even more directly essential physiological aspect of recombination has been found in its role during the replication of bacteriophage T4 (Mosig, 1983; Formosa and Alberts, 1986). The complementary role of replication during recombination has long been an important concept in deriving models for recombination mechanisms (Chapter 7 of this volume; Radding, 1982), and is suggested by numerous systems such as adenovirus (Wolgemuth and Hsu, 1981).

C. Recombination for Genetic Diversity during Development

A pivotal role for recombination also lies in its participation in rearrangements of gene families during development, as for the immunoglobulin system (Fig. 2, line H; Chapter 11 of this volume).

D. Recombination and Disease

It is now clear that certain rare recombination events are instrumental in producing human disease, including certain carcinogeneses (Adams, 1985; Lee *et al.*, 1987; Dean *et al.*, 1987; Turc-Carel *et al.*, 1987), color blindness (Nathans *et al.*, 1986), and probably one form of Alzheimer's disease (Delabar *et al.*, 1987).

E. Recombination and Evolution

The comparison of DNA sequences from various organisms has been an increasingly interesting source of information as to their relatedness and evolution. It has been a long-standing question as to whether genetic recombination between diverging species would speed or hinder evolutionary development (Turner, 1967; Ochman and Wilson, 1987; Stephens, 1985). In any case, an example of a rapid rate of genetic diversity resulting from recombination is hypothesized in the case of RNA recombination in certain viruses (King *et al.*, 1982b; Kirkegaard and Baltimore, 1986; Makino *et al.*, 1986).

In the course of this work, good evidence for past gene duplication and mutation events has also accumulated (Anderson and Roth, 1977; Campbell, 1981; Hall *et al.*, 1983; Riley and Anilionis, 1978; Rodakis *et al.*, 1984; Scott *et al.*, 1984; Stokes and Hall, 1985). The sorts of recombination events responsible, perhaps often the irregular type, have been mentioned above. A particularly interesting type of sequence relatedness which might come from, or lead to, certain rare recombination events is seen from the work of Ornston and colleagues (personal communication) and an example is shown in Fig. 7.

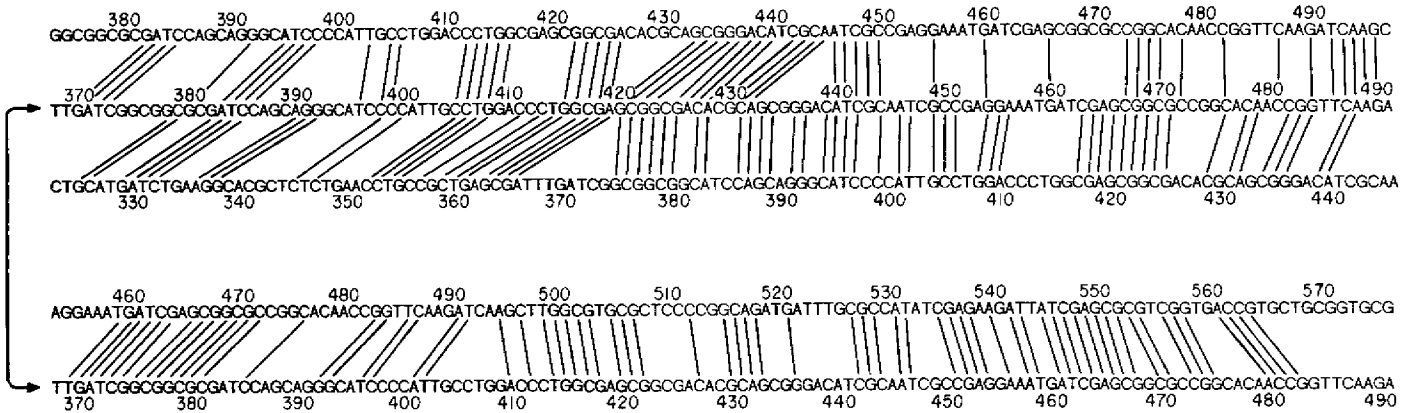


Fig. 7. Portions of the DNA sequence of one strand of the structural gene *clcB* in *Pseudomonas putida*. Partial homologies can be seen between sections displaced by approximately 10, 50, and 90 bases. These DNA sequence repetitions lead to interactions between complementary strands of DNA regions that are separated by a substantial number of residues. Mismatch repair during these interactions might contribute to sequence conservation. (From L. N. Ornston, personal communication.)

VIII. A Recombination Bibliography

Genetics Texts

An introduction to recombination is facilitated and made more meaningful in the context of genetics as a whole. Of the wide range of good genetics texts, two particular favorites that give rich, interesting, and highly readable background related to recombination are

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Suzuki, D. T., Griffiths, A. J. F., Miller, J. H., and Lewontin, R. C. (1986). "An Introduction to Genetic Analysis," 3rd ed. W. H. Freeman, New York.

Treatises on Recombination

Whitehouse, H. L. K. (1982). "Genetic Recombination. Understanding the Mechanisms." John Wiley, Chichester.

This is the closest thing to a comprehensive text on recombination currently available. The 136-page chapter on eukaryotic recombination is particularly lucid and rich in detail.

Stahl, F. W. (1979). "Genetic Recombination. Thinking About It in Phage and Fungi." W. H. Freeman, San Francisco.

Two of the beauties of this text are: first, its incisive and logical development of the nature of homologous recombination whose subtleties seem to flow naturally from first principles, using just a few recombination systems as examples, and second, the requirement that the reader, with the author's help, think analytically.

Kusher, V. V. (1974). "Mechanisms of Genetic Recombination." Consultants Bureau, New York.

This book emphasizes eukaryotic homologous recombination and includes some topics not often reviewed, such as induced recombination.

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