MOLECULAR BASIS FOR GENETIC RECOMBINATION

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THE past few decades have witnessed the successive description in biochemical—or “molecular”—terms of the great formal entities of classical genetics. The linkage group was early identified with the objectively seen chromosome, then the gene itself, in its wild and mutant forms, more and more closely related to the linear DNA regions thereof. We have seen the identification of the gene product or “physiological gene” with proteins and polypeptide units, and then the exciting unraveling of the widespread protein biosynthetic mechanisms and their control by the broadly applicable genetic code.

A last great genetic formalism—the interaction of homologous DNA regions with each other, or genetic recombination—is now coming under detailed analysis as to its biochemical mechanism. It will be impossible to summarize here details of these highly technical studies; rather I shall attempt to portray what I see as the chief principles by which answers are sought from this approach.

On the one hand, the successful unified schemes for biosynthesis and its genetic control have encouraged a dream of a single idealized process, “the mechanism of genetic recombination”. On the other hand, the comparative analysis of different genetic systems by modern geneticists has seemed to bring us a large series of different aberrations of random recombination and to suggest therefore a varied series of underlying mechanisms. It will be my purpose to argue here that these are indeed visualizable as merely various manifestations of a broadly uniform genetic process, modified only in non-essential ways by the diverse enzymatic endowments of the different organisms and systems.

What are in fact the various so-called abnormalities of recombination—the map distortions, map expansions, non-additivities, positive and negative interferences, gene conversions and polarities? All of them can be described as the observance of a greater or lesser number of recombinants *within a particular subpopulation* than were expected, on some previously assumed basis. As a single example, let us recall that gene conversions are properly claimed when a full recovery of primary segregants, from meiosis in an ascomycete or an attached duplication, shows one parental allele—or small region—in excess over its homolog. Now, we do not have the right to claim gene conversion in these or other organisms, when the primary products are submerged in a population that is derived from mass matings. But let us suppose we have so interacted two genomes

ABCDE   and   abcde

as in Figure 1. Now let us suppose that among recombinants of the constitution aBCde a proportion experienced a biochemical event equivalent to gene conver-

proportion of cases the complex would have been resolved in a double crossover, of such limited extent that the whole exchange would appear to be non-reciprocal, like the initiating conversion at its margin.

The apparent equal choice between an extreme short-range crossover and an orthodox reciprocal crossover determined by the distance suggests that in the original complex some alternative binary choice predominates over distance in determining the mode of resolution. The author has proposed (HOTCHKISS 1971) that this binary choice may be a strand selection of one of two DNA strands (or two homologs from four) for incision and "repair" from an inter-strand complex. Equivalent suggestions have recently been made by others, particularly by STAHL (1969), by SIGAL and ALBERTS (1972) and by SOBELL (1972). Other models achieve crossover and non-crossover configurations through rejoining at adventitious preformed breakpoints in the different strands (e.g., BROKER and LEHMAN 1971).

Our first proposal, then, is that conversion-like events may initiate recombinations, in which case the conversion would occur at one end of the recombined region. Although recognized conversions are of variable extent, they are always limited (FOGEL and MORTIMER 1969), so they would only rarely coincide with regions bearing markers and in a system in which conversion might be assayed. Thus if one looks for conversions, one finds a high proportion of accompanying recombinations, while if one is looking at recombinations one may be overlooking all but a very few of the conversions that may be associated. In mating within mass populations any such conversions which do involve markers would, as already indicated, appear merely as additional recombinants within certain intervals, and therefore either be accepted or reported as one or another form of map distortion.

In this light question (2) appears more plausible, according to which the conversion event is not the initiating occasion for a few recombinations, but the genetic manifestation, usually missed or overlooked, of a biochemical event occurring at the margin of perhaps all recombinational crossovers. This has been specifically suggested by PASZEWSKI (1970) and by the author (HOTCHKISS 1971, 1973). In what follows such a biochemical event will be considered to be a "molecular conversion" resulting from an unequal copying of parental DNA strands needed to bring interacting strands in register before they can break and rejoin their homologs.

Molecular Models for a Recombination Process

A great many models and mechanisms have been presented for genetic recombination; in earlier years they were formal ones simply restating the observations, but more recently increasingly realistic ones taking into account the properties of DNA helices and in some very recent cases, the demonstrated properties of the DNA-modifying enzymes presumed to be involved. It will be manifestly impossible to summarize here these mechanisms in any except the broadest terms.

An early distinction between breakage-reunion and copy-choice mechanisms has all but disappeared. With demonstration of actual strand insertions, the copy-choice role, when retained at all, is relegated to an "adjustment synthesis" making possible exact strand-to-strand fit and register. This compromise was long ago foreshadowed in suggestions by PRITCHARD (1960). Beginning with the proposals of WHITEHOUSE (1963), of HOLLIDAY (1964) and of WHITEHOUSE and HASTINGS (1965), models have exploited the double-strand nature of DNA in postulating association of single-strand components from one helix with those of another by base-pairing in "hybrid DNA", without severing a double helix as such. In fact, a principal distinction between most current models is the way in which several single-strand breakages and junctions are imagined to occur.

Recombination between two double helices virtually requires at least four strand openings—and more if later repair steps are postulated. In these first molecular models the points of strand opening were somewhat arbitrarily assumed (being exactly opposite or otherwise convenient to the purposes). In some recent models the writer and others (BOON and ZINDER 1969; PASZEWSKI 1970; SIGAL and ALBERTS 1972) have entertained the more general possibility of staggered points of strand breakage, producing asymmetric complexes and therefore unidirectional sequences of events. It has even been proposed that an initial breakage in one strand triggers events producing all subsequent breakages and joinings (HOTCHKISS 1971). In these models a polarized or asymmetric outcome can be the result of an asymmetric early event rather than of an asymmetric resolution from a symmetric complex as required by earlier formulations.

Many genes and gene products (polymerases, exonucleases and ligases) impinge their effects upon recombination processes. Some are discussed in accompanying papers of this Symposium. Others described in recent literature show specialized effects upon recombination of specific regions. These signs should be warning enough that there will be many enzymes which can, under various conditions, modify the events of recombination. Thus, any unity there may be in recombination mechanisms will clearly depend upon the relative uniformity of DNA structure in different organisms, and we must ask to what extent the various enzymes affecting it merely alter the rate of basically similar processes and to what extent they institute essentially *new* processes.

After assuming various strand breakages, convenient to the purposes and the results to be predicted, the model builder begins to make use of the armamentarium of modern biochemistry. Usually DNA degradation (gap widening by exonucleases) much as in post UV-repair, and strand elongation are included (polymerase) and appropriate chain joining (DNA ligase) are included *ad libitum*. There are numerous physical evidences and indeed biochemical-mutation studies to show that such steps are really occurring. Labeled intermediates fitting some of the expectations have been successively revealed in a series of studies with the T-even coliphages (TOMIZAWA and ANRAKU 1964; ANRAKU and TOMIZAWA 1965; KOZINSKI, KOZINSKI and JAMES 1967; ANRAKU and LEHMAN 1969; ANRAKU, ANRAKU and LEHMAN 1969; BROKER and LEHMAN 1971). "Joint molecules" having components from two parental DNA's have also been demon-

strated in transformed pneumococcal populations (FOX and ALLEN 1964; FOX 1966) and in *Bacillus subtilis* populations (BODMER and GANESAN 1964; BODMER 1966; LAIRD, WANG and BODMER 1968; DUBNAU and DAVIDOFF-ABELSON 1971; PIECHOWSKA and FOX 1971; HARRIS and BARR 1971) and *Hemophilus influenzae* (NOTANI and GOODGAL 1966; STUY 1965).

The studies of transformed bacteria just mentioned indicate a recombination intermediate in which the molecular segment of donor DNA incorporated into a recipient helix is a limited region of single DNA strand. Partial homogenization by repair of this heteroduplex (EPHRUSSI-TAYLOR and GRAY 1966; LOUARN and SICARD 1968; TIRABY and FOX 1973) have been postulated. When the donor itself is a heteroduplex it can apparently be homogenized before incorporation (ROGER 1972) or even without incorporation (SPATZ and TRAUTNER 1970). But the studies with T-even phages mentioned, and a series of fundamental ones with the temperate λ -coliphages (MESELSON and WEIGLE 1961; KELLENBERGER, ZICHICHI and WEIGLE 1961; MESELSON 1964; STAHL *et al.* 1972; WHITE and FOX 1974) have indicated what seems to be a different kind of primary recombinant DNA—one bearing extensive double-stranded segments from each parent, probably joined at a heteroduplex overlap.

Clearly these different results (and any such differences) in some sense imply different mechanisms. But need the mechanisms be different in principle—qualitatively different—or only differing in the extent or balance of different processes constituting the whole? The part played by DNA degradation (and synthesis) is another feature differentiating existing recombination models. The DNA that is trimmed out in excision or repair presently serves as a degree of freedom (like an extra mathematical variable in a theoretical equation) permissively allowing one to replace that DNA with a copy from the same or a different template—and thus arrive at a foreknown result. In my opinion it would be much better if we could forge our assumptions from expectations of what the enzymes are likely of themselves to do.

A Model with Initial Asymmetric Steps

It has seemed to me likely that a single strand break would permit an “attack”—not by any means always successfully propagated—by that single strand upon an adjacent helix (Figure 2). The spontaneous dissociation or “breathing” of the DNA strands, together with the pronounced affinities for single strands of such enzymes as DNA polymerase (KORNBERG 1969) and the several proteins similar to the gene 32 protein (ALBERTS and FREY 1970) should make this migration of DNA strand ends sometimes effective. Base pairing, like that of RNA transcripts, should allow the “donor” strand to lie in the wide helical groove, holding at intervals to the “recipient” DNA strand. If the migrating end is a 5' strand end, there is not much it can do, and it will doubtless soon be degraded for some distance and eventually sent back home. If it is a 3' strand end, DNA polymerases, probably already bound to it, will be able to lengthen it, like an RNA transcript, along an homologous complementary template, with which it

FIGURE 2.—Model of an asymmetric attack by a DNA strand upon an homologous recipient helix.—The lower pair in each figure (heavy lines) is considered as a donor helix, nicked at A, and attacking the recipient (upper) helix by partial hydrogen bonding along $b-b'$. The arrow indicates the polarity of the 3' strand ends, along which complementary synthesis (dashed line) increases the possibility of an eventual "repair" by incision of the attacked homolog at a point a' and release of a new 3'-end (strand $c-a-a'$) to counterattack the original donor at a point to the right of A (or A').

has paired. If the homologs are not genetically identical an extra copy of some region will have been made (e.g., region a , Figure 2).

If copying by the polymerase has been extensive and rapid enough, at some point, say a' , one strand of the attacked, or recipient, helix will have a finite chance of accepting stable bonding with this maverick strand. Soon a DNA-repair system should detect that the two strands competing for pairing with a third over the region $a-a'$ are physically mispaired and open up one of the competing strands. If a fraction of the time the recipient strand is broken in this repair, a single-strand crossover will have been produced. The released recipient strand, also having a 3' end, will be in position to attack the donor helix—but note that it is going to attack even farther to the right of a' and 3'-wards of the original break.

Briefly, an equivalent event in the lower helix, to the right of A, would lead to a doubly bridged pair of helices by joining at the gaps (bottom, Figure 2; also Figure 3). In short, these successive attacks have led to a physically symmetrical crossover in one strand of each helix, superficially like a HOLLIDAY (1964) figure. But note, however, that in a genetic sense, it has from the beginning been non-reciprocal, because the strands have crossed over at different levels, and a unilateral conversion region has already been produced, by extra copying (rather

FIGURE 3.—Effect of relative activities of incision-excision and of polymerase systems upon extent of the non-reciprocal exchange.—In the upper figure an incision system, accompanied probably by some excision, has responded to the strand mispairing in the region a' , before polymerase has extensively lengthened the attacking strand. In the lower figure, polymerase activity has been more extensive and incision has released a longer region of the upper homolog, producing a more extensive conversion over whole region $a-a'$.

than later by asymmetric repair). The conversion is the result of the adjustment synthesis which copied the upper template upon the attacking strand end and of the preservation and extension of both this 3'-end and the subsequently released one at a' . Let me here only summarize my proposal for resolution of this intermediate by suggesting that a new repair incision would be stimulated, allowing one or another of the crossed strands to repeat the attack, insertion, lengthening and joining as already described.

Some regions of heterozygous overlap will have been produced—although fewer than in the HOLLIDAY and other models based upon obligate or predetermined sets of breakage points—because the adjustment synthesis I assume involves already a partial “repair” aspect. Homogenization of genetic heteroduplex regions can be assumed as in other models to fix or reverse the chromatid conversion.

In particular, note that relative enzyme rates, not DNA distance, have determined the point of successful rejoining at A' (below). If the polymerase is less active and the repair incision occurs early we will have an earlier rejoining (Figure 3, upper part). Here we can see that the extent of conversion and the actual site of the crossover return in the second junction are determined by *relative enzymatic rates*. The polymerase will tend to lengthen the intervals, (Figure 3, lower part), and activity of the incision repair system to shorten it. Also, within the population of recombinants, the exchanges should illustrate a poten-

RECOMBINATION EVENTS ARE PROPORTIONAL TO:

$$(\text{probability for initial nick}) = f(\text{distance})$$

EXTENT OF CONVERSION AT BORDER OF RECOMBINATION:

$$(\text{nick probability}) \times \frac{\text{polymerase span}}{\text{incision probability}} = f(\text{distance}) \times (\text{physiological index})$$

FIGURE 4.—Quantitative expression of the probability for recombination or conversion.

tial *polarity* (relative to any particular initial nick)—by virtue of the unidirectional attack process, and the 3'-direction of all known unitwise DNA synthesis.

These assumptions, summarized in Figure 4, suggest that the classical dependence of recombination upon distance may be laid to the probability for the initial triggering DNA strand nick. But the conversions, and resulting aberrant ratios, may depend upon a more complex quotient of two "physiological distances" itself sometimes varying from one cell line or one condition to another. These distances are pictured as the most probable span of DNA length within which the polymerase or incision systems will normally act.

This sequence already illustrates my thesis that the different results of recombination in different systems may be expected from a common pathway, through the effect of different enzymatic levels of activity. It should be pointed out that single donor and return strand insertions as pictured above are approximately equivalent to a one-armed replication fork, or to a branch migration by a single strand, and they therefore share properties included in some other models. Of course, a wider variety of rates and conditions such as mispairing or mismatch which lead to repair would have to be assumed, to cover the full range of observed recombinational exchanges in all systems.

As a brutally brief summary of the active investigation of DNA synthesis involved in recombination, let me merely note that recombinants appear to be formed when very little DNA synthesis is occurring (HOTTA and STERN 1971) or permitted (BOON and ZINDER 1970; WHITE and FOX 1974) but restriction of DNA synthesis may restrict the pattern of recombinations which do occur (STAHL *et al.* 1972).

Resolution of Recombination Intermediates

This short treatment of models would be incomplete without a few more words on the resolution of the various cross-bridge intermediates postulated. Several workers within the last two or three years have noticed that a certain physical symmetry of bridge strands exists in this stage (even when genetic asymmetry has been postulated). This has led to proposals of simple lateral migration of the bridge region. (HOTCHKISS 1971; SIGAL and ALBERTS 1972) or of double-strand branches (BROKER and LEHMAN 1971) until strand breakages random with

respect to strands are induced by repair systems (HOTCHKISS 1971) or adventitious preexisting breaks are reached. Because of the strand equivalence, it is pointed out that the alternation of bridged and unbridged strands can easily occur (SIGAL and ALBERTS 1972). All of these and various other workers have seen these symmetries (further discussed and extended by SOBELL 1972) as the molecular basis for the equal probability of the return to the same pair (no outside marker recombination) or to the opposite pair of strands (outside marker recombination).

It seems that older models tended to involve random or symmetrical initial events, followed by the necessity for somewhat unexplained asymmetric resolution steps. By contrast, we now have considerable emphasis on the possible symmetry of the late resolution steps. In the case especially of the author's model, and that of PASZEWSKI (1970), the asymmetric results are seen as proceeding inevitably from the asymmetric intermediate determined by the location of initial one-strand breakages, and in the model of BOON and ZINDER (1969), similarly, by three initial strand breaks.

The recombination model described above leads to some testable predictions. Our preliminary quantitative description (Figure 4) suggests that first order distance will often account for the frequency of recombination events, but that when it does not, a physiological quotient may be modifying the probabilities. This quotient would not be a constant, especially when availability or activity of certain enzymes is altered by mutation, or by physiological changes (as perhaps in male *Drosophila* where recombination does not occur), or when precursors for DNA synthesis are available in greater or lesser degree. The nature and magnitude of the mismatch or misfit pictured as leading to incision would also have a bearing on frequency. From any given initiating site, non-reciprocal "exchange" would be expected, insofar as markers are sufficient, extending 3'-wards in the involved strand to a margin beyond which the exchange is reciprocal. The occurrence of the non-reciprocal exchange region would be inversely related to its length, therefore showing polarity with respect to any initial site for which there was a selection or a predisposition for breakage. The qualitative possibility for polarity would, as seen above, be attributable to the 3'-directionality of strand elongation.

That strand ends may lead to what is described above as "attack" upon more or less intact homologous DNA is supported by various observations from the areas of bacterial transformation, bacterial and viral recombination recently summarized elsewhere (HOTCHKISS 1973). It is also to be noted that the results of WHITE and FOX (1974) indicate a recombination intermediate in λ with precisely the polarity (3'-ends in a heteroduplex) postulated here.

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