SYMPOSIUM NO. 5: GENETIC EXCHANGE

Introduction by the Chairman

ADVANCES IN RECOMBINATION RESEARCH

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IN the ten years since I last addressed an International Congress of Genetics, considerable progress has been made in understanding the process of recombination, and yet many of its central features still elude us. I would like to summarize briefly some of the main advances of the last decade, and to indicate where these discoveries seem to be leading us.

An outstanding advance was the demonstration by TAYLOR (1965) that chiasmata correspond to points of breakage and rejoining, as shown by ^{3}H-thymidine labelling. This experiment provided the first direct evidence that crossing over was by breakage and joining, more than 50 years after MORGAN had first demonstrated the process. Any suspicion that TAYLOR's conclusion was falsified through the occurrence of sister-chromatid exchange has been eliminated by the experiments of PEACOCK (1970) and JONES (1971). Of course, breakage and rejoining had already been established for prokaryote recombination, initially in the classic experiments by MESELSON and WEIGLE (1961) and by KELLENBERGER, ZICHICHI and WEIGLE (1961) with phage lambda of *Escherichia coli*, and subsequently in transformation studies by Fox and ALLEN (1964) and by BODMER and GANESAN (1964) with *Diplococcus pneumoniae* and *Bacillus subtilis*, respectively. That recombination has been shown to occur by breakage and rejoining does not mean that break-and-copy is ruled out. Such models invoke breakage of a nucleotide chain followed by its extension using a complementary chain from the other parent as template, and have been favored by BOON and ZINDER (1971) for phage f1 of *E. coli*, and by STAHL *et al.* (1972) for the general recombination in lambda. On the other hand, the idea that break-and-copy mechanisms operate in eukaryotes (e.g., PASZEWSKI 1970) has little evidence to support it, as the studies by LEBLON and ROSSIGNOL (1973) with *Ascobolus immersus* have shown.

Much new evidence has been obtained recently for correction of mismatching of bases in hybrid DNA. First suggested by HOLLIDAY (1962), it has been favored ever since as an explanation for conversion in eukaryotes, but in prokaryotes its occurrence has been questioned until recently. EPHRUSSI-TAYLOR and GRAY (1966) proposed such correction to account for the low integration efficiency of some mutants in pneumococcal transformation, and HOGNESS and co-workers (HOGNESS *et al.* 1967; DOERFLER and HOGNESS 1968) obtained evidence for it in phage lambda from ingenious experiments using heteroduplex molecules prepared *in vitro*. But the idea of mismatch repair in prokaryotes did

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not gain wide acceptance until TRAUTNER and associates (SPATZ and TRAUTNER 1970; TRAUTNER *et al.* 1973) carried out transfection experiments with phage SPP1 of *Bacillus subtilis*. They concluded that, depending on the mutant, either the neighboring base sequence or the molecular nature of the mismatch influenced the correction process. The experiments of BENZ and BERGER (1973), demonstrating selective allele loss from mixed infections of *E. coli* with wild-type phage T4 and rII mutants, add further evidence for the widespread occurrence of excision of mismatched nucleotides.

In eukaryotes, the correction hypothesis has been much strengthened, first, through the finding by ROSSIGNOL (1969) that spore color mutants of gene 75 of Ascobolus fall into discrete classes with characteristic frequencies of conversion to wild type and to mutant; and secondly, through the discovery by LEBLON (1972a) that conversion pattern in Ascobolus depends on the mutagen used to obtain the mutant, and furthermore (LEBLON 1972b) shows a pattern in intragenic revertants of frameshift mutants complementary to that of the original mutant. Such results are expected if the enzyme presumed to recognize mispaired bases is sensitive to the molecular nature of the mismatch. In *Saccharomyces cerevisiae*, on the other hand, no mutant is known in which conversion to wild type and to mutant differ in frequency (FOGEL and MORTIMER 1969). Evidently, the correcting enzyme in yeast is unable to recognize different kinds of mismatching.

Co-conversion—the linked conversion of two or more mutants—was first demonstrated by CASE and GILES (1964) with Neurospora, and has been shown by FOGEL and co-workers (FOGEL and MORTIMER 1969; FOGEL, HURST and MORTIMER 1971; HURST, FOGEL and MORTIMER 1972) with Saccharomyces to decrease in frequency, relative to the frequency of single-site conversion, with increasing distance between the mutant sites. This result is neatly explained by the hypothesis that excision is extensive in the correction of mispairing, with a modal length estimated by them to be several hundred nucleotides.

GUTZ (1971) with *Schizosaccharomyces pombe* and LEBLON and ROSSIGNOL (1973) with Ascobolus discovered that mutants showing frequent and biased conversion (for example, to mutant more often than to wild type) imposed a correspondingly increased frequency and bias on the conversion of alleles in two- and three-point crosses. An Ascobolus mutant with a high frequency of postmeiotic segregation, on the other hand, did not impose such segregation on an allele that lacked it. These results are precisely those expected if conversion results from extensive excision triggered by certain kinds of mismatch, and if postmeiotic segregation is a failure of such excision.

Extensive excision will also explain map expansion and the dependence of the recombination frequencies of alleles on the distance between the sites (FINCHAM and HOLLIDAY 1970).

In a cross of two closely-linked mutants, asci with half the products of meiosis wild-type, implying conversion to wild type for both mutants, are usually very rare. TOURÉ (1972), however, found such asci to be relatively frequent (up to 9% of the recombinant asci) in several crosses of mutants of spore color gene *14*

in *Podospora anserina*. In a cross between two mutants, *B7* and *C18*, of the *grey-5* gene of *Sordaria brevicollis*, I have found that over 20% of the recombinant asci (115 out of 534) have 4 wild-type spores. Such asci require correction of mispairing in hybrid DNA at the site of one mutant in one chromatid and of the other mutant in the other chromatid. TOURÉ found that Podospora crosses which give this type of ascus correspond to relatively short chromosome segments. Presumably with longer intervals it is rare to have the particular distribution of hybrid DNA required.

The simple idea which I proposed 10 years ago, that hybrid DNA is of equal extent in the two chromatids, fails to explain the rarity of reciprocal conversion. The central question of why recombination within the gene is so often non-reciprocal is still unanswered. This question is exemplified by the data of STADLER and TOWE (1971) with the *w17* spore color gene in *Ascobolus*. SOBELL (1972) has suggested that a nuclease nicks one chain in each duplex when a mutant enters hybrid DNA, and that the enzyme also has exonucleolytic activity and degrades one of the two nicked chains. This would mean that hybrid DNA was then largely confined to one chromatid. There is precedent for combined endonucleolytic and exonculeolytic functions in the *recBC* DNase of *E. coli* (GOLDMARK and LINN 1972).

The extensive studies by CHOVNICK and co-workers (CHOVNICK, BALLANTYNE and HOLM 1971; BALLANTYNE and CHOVNICK 1971) with the maroon-like and rosy genes of *Drosophila melanogaster*, and of CARLSON (1971) with the rudimentary locus, have established that the recombination mechanism in Drosophila shows many of the same phenomena as in fungi. This is an important advance, and means that conclusions drawn from fungal studies are likely to apply to eukaryotes generally.

The initial steps in eukaryote recombination are still obscure. CATCHESIDE and associates (JESSOP and CATCHESIDE 1965; CATCHESIDE 1966; SMITH 1966; ANGEL, AUSTIN and CATCHESIDE 1970; CATCHESIDE and AUSTIN 1971) discovered dominant repressors of recombination in Neurospora. These affect specific limited regions of the chromosome unlinked, in general, to the repressor locus or to one another. The polarity of recombination, as well as its frequency, is affected by these repressors in the way expected if they act to prevent hybrid DNA formation from particular initiation points. But whether each repressor acts through controlling the formation or the activity of a specific endonuclease, as ANGEL, AUSTIN and CATCHESIDE (1970) suggested, is uncertain. Another possibility is that recombination in eukaryotes is initiated at the premeiotic S phase (HASTINGS 1964), perhaps through failure to complete the DNA synthesis (WHITEHOUSE 1967, 1972). There is support for this from a number of sources (DAVIES and LAWRENCE 1967; HOTTA and STERN 1971a; GRELL 1973), including the study by CHIU and HASTINGS (1973) of the effect of phenethyl alcohol and other inhibitors of DNA synthesis on recombination in *Chlamydomonas reinhardii*. If recombination is initiated only at unjoined replicon ends, each recombination repressor might bind to specific ends in such a way as to prevent the formation of hybrid DNA from these points.

Turning to prokaryotes, a development of great importance has been the evidence obtained by HOWARD-FLANDERS and co-workers (RUPP *et al.* 1971; HOWARD-FLANDERS, LIN and COLE 1973) for a pathway involving recombination in the repair of damage to *E. coli* and lambda prophage DNA caused by UV-induced pyrimidine dimers and by photochemical cross-linking by psoralen. It seems that recombination has significance in evolution for the survival of the cell as well as for the genetic diversity of progeny. Evidence is now accumulating pointing to recombination repair also in eukaryotes (HOLLIDAY 1967, 1971; HUNNABLE and COX 1971; JANSEN 1970; FORTUIN 1971). HOWARD-FLANDERS *et al.* have concluded that a DNA molecule containing certain types of structural damage can initiate genetic exchange by interacting with an undamaged homologous molecule. This is similar to the picture drawn by HOTCHKISS (1971), who has likened a broken single nucleotide chain peeling away from a duplex molecule to a poisoned arrow, the poison being a coating of DNA polymerase. Clearly, these ideas could be relevant to recombination generally.

The demonstration by KUSHNER, NAGAISHI and CLARK (1972) and CLARK (1973) of at least two recombination pathways in *E. coli* has drawn attention to the fact that alternative pathways can evidently have a selective value for a process as important as recombination for the survival both of the individual and of the population.

The isolation of two recombination enzymes—the *recBC* DNase, already referred to, and the lambda exonuclease—and the progress in understanding how they function in recombination (GOLDMARK and LINN 1972; KUSHNER, NAGAISHI and CLARK 1972; CASSUTO and RADDING 1971; CASSUTO *et al.* 1971) has begun to lay the foundations for an understanding of the biochemistry of the process. The discovery by HOWELL and STERN (1971) that at zygotene and pachytene in Lilium pollen-mother-cells an endonuclease, a polynucleotide kinase and a polynucleotide ligase are present, but are absent at other times, provides strong circumstantial evidence for their involvement in recombination. Highly significant, also, is the finding at this stage of meiosis in Lilium and in mammals (HOTTA and STERN 1971b,c) of a protein similar in properties to the product of gene 32 of phage T4. The gene-32 protein has been shown by ALBERTS and FREY (1970) and by DELIUS, MANTELL and ALBERTS (1972) to bind to single-chain DNA so as greatly to extend the normally folded chain, and the meiotic protein seems to be similar. The part played by these protein molecules in recombination is not known, but it seems likely that they facilitate complementary base pairing, such as is required for heteroduplex formation. In T4, ANRAKU and TOMIZAWA (1965) showed that the nucleotide chains from the two parents initially form a non-covalent joint molecule, and that the parental duplexes are later joined covalently to give a recombinant molecule. BROKER and LEHMAN (1971) discovered that branched duplex molecules were intermediates in T4 recombination, the gene-32 protein evidently facilitating the formation of the heteroduplex structures believed to form the branches. According to their hypothesis, endonucleolytic and then exonucleolytic activity would precede the hybrid DNA formation, and nucleases, DNA polymerase and ligase would need to act after-

wards. The part played by polynucleotide ligase in controlling recombination frequency in T4 has been demonstrated by KRISCH, HAMLETT and BERGER (1972). With low levels of ligase, DNA synthesis generates highly nicked molecules which are recombinogenic.

The prokaryote recombination mechanisms seem likely to reveal a number of variations on the break-and-join and break-and-copy themes, and probably none will be quite like the eukaryote mechanism. The reciprocal recombination in the integration of the lambda genome into the *E. coli* chromosome (SIGNER 1968; ECHOLS 1971) seems to involve so short a region of homology between host and viral chromosomes (DAVIS and PARKINSON 1971) that the process probably has little relevance to reciprocal recombination in eukaryotes. The discovery of linkage and recombination between characters in *Chlamydomonas reinhardii* apparently determined by the chloroplast DNA (SAGER and RAMANIS 1965, 1967, 1970; SCHLANGER, SAGER and RAMANIS 1972), and likewise with yeast characters determined by the mitochondrial DNA (THOMAS and WILKIE 1968; WILKIE and THOMAS 1973; COEN *et al.* 1970; BOLOTIN *et al.* 1971; RANK and BECH-HANSEN 1972; RANK 1973) is an exciting development to which prokaryote recombination mechanisms could have direct relevance.

Three approaches to eukaryote recombination look particularly promising. Firstly, FOGEL, MORTIMER and their associates have developed techniques for isolating large numbers of recombination-deficient mutants in yeast using disomic strains. Comparison of the behavior of mutants selected for meiotic recombination deficiency (ROTH and FOGEL 1971) with those selected for mitotic recombination deficiency (RODARTE-RAMÓN and MORTIMER 1972; RODARTE-RAMÓN 1972) promises to reveal the extent to which these processes share a common pathway, and the part they play in DNA repair.

Secondly, and complementary to these studies, nuclease-deficient mutants have been isolated in *Ustilago maydis* by HOLLIDAY and HALLIWELL (1968) and by BADMAN (1972). BADMAN found that crosses deficient for both an extracellular and an intracellular DNase showed no conversion, but crossing over was apparently of normal frequency.

Thirdly, the isolation of meiosis-deficient mutants, which has been achieved in several fungi, shows promising results. SIMONET and ZICKLER (1972) found that mutants of gene *mei2* in *Podospora anserina* are blocked before pachytene. SIMONET (1973) found, however, that a mutant of this gene is leaky. When crossed with alleles it caused a decrease in interference between crossovers, and an increase in intragenic crossing over relative to conversion. The hypothesis of interference which I favor (WHITEHOUSE 1967b, 1972) predicts a similar result, namely, that a decrease in its intensity will be associated with an increase in the frequency of crossing over relative to recombination events associated with parental flanking markers.

Hopefully, the pursuit of these various approaches, together with the further analysis of the behavior of fungal spore color mutants spanned by outside markers (KITANI and OLIVE 1967, 1969; STADLER, TOWE and ROSSIGNOL 1970; STADLER

and TOWE 1971; AHMAD, BOND and WHITEHOUSE 1972) will soon give us a clearer picture of the recombination mechanism.

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