Perspectives

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The Holliday Junction on Its Thirtieth Anniversary

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IN the 1940s and 50s, the apparent lack of reciprocality in the production of bacteriophage recombinants led to the ascendancy of copy-choice schemes for recombination in those little creatures (STURTEVANT, cited in HERSHEY and ROTMAN 1949). The subsequent description of gene conversion (non-4:4 meiotic segregation) in Neurospora (MITCHELL 1955a,b) was viewed by some as an illustration of the applicability of such schemes to meiotic exchange (*e.g.*, FREESE 1957).

However, to ROBIN HOLLIDAY, copy-choice was not a decent explanation for meiotic conversion. He found the potential for a different explanation in the embryonic field of DNA repair. The trick was to make recombination involve a heteroduplex, in which a marked segment of one chain carries information from one chromosome while the corresponding segment of the other chain carries information from its homolog. [The word "strand" is used by classical geneticists to denote a chromosome or a chromatid. It is used by those lacking a classical education to refer to a polynucleotide chain as defined by WATSON and CRICK (1953). We'll avoid confusion by not using it at all.] Such locally heteroduplex products of recombination had been hypothesized to account for heterozygous particles of phage T4 (LEVINTHAL 1954). Then, enzymes analogous to enzymes proposed to repair UV damage could recognize violations of Watson-Crick pairing at the marked site and operate on the heteroduplex, removing a bit from one chain or the other. Deviations from 4:4 segregation would (or, at least, could) result. Failure of the hypothetical mismatch correction enzymes to operate on a given heteroduplex site would result in meiotic products that would segregate alleles in the first post-meiotic mitosis. The demonstrated occurrence in some fungi of such post-meiotic segregations (PMS) fully justified the assumption of heteroduplexes in meiotic recombination.

In fungi, about half of the tetrads manifesting either deviations from a 4:4 ratio (conversion) or 4:4 tetrads with PMS at a given site in two of the four haploid products are reciprocally recombined for markers flanking that site (they are usually tetratype for those markers). The crossover typically involves the chromatid that is converted or the two chromatids that are enjoying PMS. The remaining tetrads are parental type (*i.e.*, nonrecombinant ditype). The apparent equality of these two types (the precision of which was later shown to be bogus) provoked the notion of a structurally symmetric four-chained intermediate that could be resolved to give crossover or noncrossover chromatids with equal probability. The structure proposed by HOLLIDAY (1964) fit the bill in all essential respects. It was, as HOTCHKISS (1974) exclaimed, "... the only sophisticated way in which two homologous DNAs can become covalently joined."

Wed to the classical notion that crossing over is a reciprocal process, HOLLIDAY envisioned processes for forming and for resolving the Holliday junction intermediate that were symmetric at each step. Thus, he proposed that chains of the same polarity were simultaneously cut on homologous chromatids at the same site (Figure 1). Each cut chain was then unwound on one side of the cut and rewound on the complementary chain vacated by the other. The four-chained structure (the Holliday junction), which could be modeled in a tidy way (SIGAL and ALBERTS 1972), was resolved either by cutting the pair of chains that were swapped (to give chromatids that were parental for flanking DNA) or by cutting the other two chains (giving chromatids that were recombinant for flanking DNA). The structural symmetry that could underlie equality for these two modes of resolution was specified by SOBELL (1974), who noted that the swapped and unswapped chains could exchange positions by isomerization of the structure through the open, four-way junction intermediate visualized in phage T4 by BROKER and LEHMAN (1971).

HOLLIDAY's model had attractive features beyond those specifically identified by him. (i) The two-step feature of the model was nice. First, the Watson chains (say) could be cut. They could then engage their partners' Crick chains to verify that the cut sites on the two participants were truly homologous. If they were, permanent partner swapping could be effected. If they were not, each could retreat to its old partner with no harm

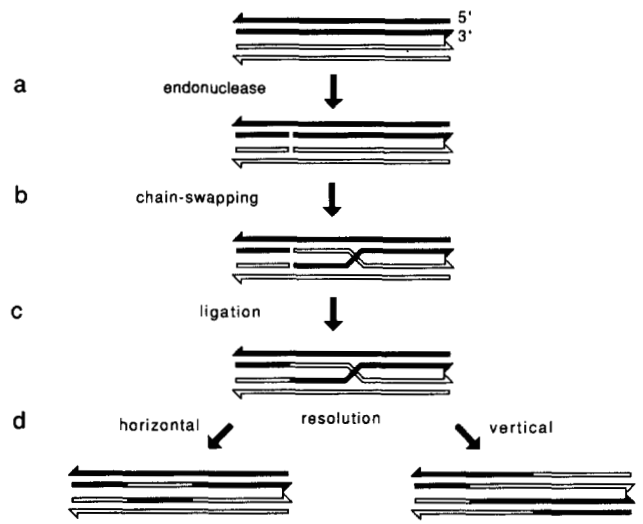

FIGURE 1.—The Holliday model. (a) Paired homologs are cut at the same level on corresponding chains. (b) The cut chains swap pairing partners. (c) Nicks are ligated, completing the formation of a Holliday junction. (d) The four-chained intermediate is resolved either by cutting the two swapped chains ("horizontal") or by cutting the two originally unswapped chains ("vertical"). Products are ligated. Horizontal resolution produces a pair of duplexes that are parental except for the short region in which they have swapped single chains (patches). The patches will be heteroduplex if the two parents differed in the patched region. Vertical resolution produces a pair of crossover duplexes that are spliced together. The splice will be heteroduplex if the two parents differed in the spliced region. Conversion can result from mismatch correction operating on heteroduplex patches or splices.

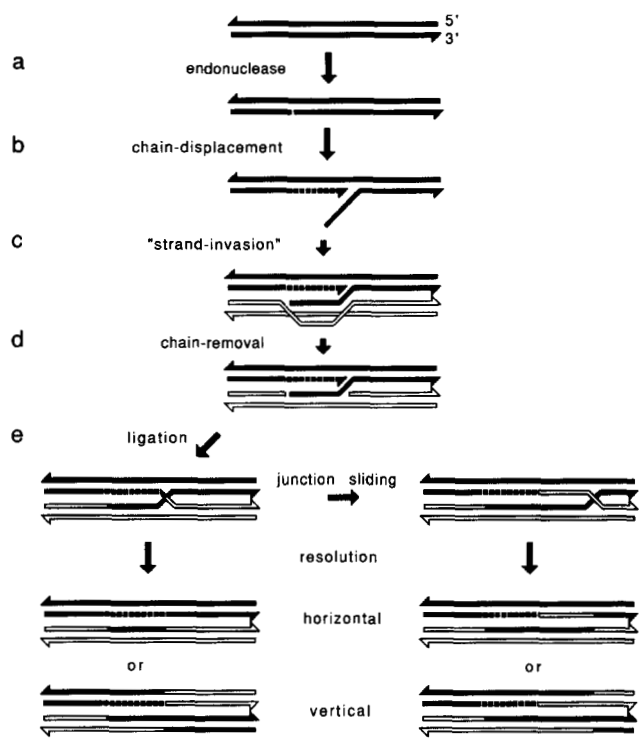

FIGURE 2.—The Meselson-Radding model. (a) A duplex is cut on one chain. (b) DNA polymerase operates in the chain-displacement mode. (c) The resulting single chain invades the homolog, displacing its counterpart. (d) This displaced chain is enzymatically digested. (e) Ligation completes the formation of a Holliday junction, which is genetically asymmetric in that only one of the two duplexes has a region of potentially heteroduplex DNA. If the junction slides, heteroduplex DNA can arise on both duplexes. (f) Resolution of the junction occurs as in the Holliday model.

done. (This feature of the model might not have struck ROBIN as very relevant. He had apparently envisioned a prerecombinational pairing of homologs that was sufficient to avoid such embarrassments.) (ii) The requirement that the initiating cuts be precisely isolocal could be relaxed. Once chain swapping had been effected, appropriate enzymes could trim or fill as necessary. (However, such trimming and filling could be a source of gene conversion, and ROBIN was conspicuously reluctant to allow for any conversion mechanisms other than mismatch correction. In fact, his adherence to that perspective often led him to equate the words "correction" and "conversion.")

Like any truly fine model, ROBIN's was testable. The structural symmetry in each of the steps and in the intermediate predicted symmetric consequences. In his model, heteroduplex DNA on one chromatid is invariably accompanied by heteroduplex on the other. Evidence of this symmetry might be lost through mismatch correction, but shadows of the initial symmetry would be likely to remain in the resulting types of tetrads. Data from some fungi supported the model. However, as data on yeast tetrads were released (mostly from the laboratories of SY FOGEL, BOB MORTIMER and PHIL HASTINGS), it became apparent that HOLLIDAY's model was too symmetric to deal with data of *Saccharomyces cerevisiae*, in which little or no evidence of reciprocal heteroduplex could be found (but see ALANI *et al.* 1994).

Rather than abandoning the possibility of a universal recombination mechanism, MATT MESELSON and CHARLEY RADDING (1975) altered ROBIN's model to give it the flexibility required to handle data both from yeast and from fungi that did show appreciable reciprocality in heteroduplex formation (Figure 2). In their model, a recombinogenic single chain was displaced from a chromatid by the action of polymerase operating in the chain-displacement mode. This chain invaded the homolog (exploiting the supercoiled nature of the latter and/or using the as yet to be discovered "strand-invasion" activity of RecA protein), displacing the resident chain of like polarity. Nuclease activity was postulated to remove this displaced chain, and a genetically asymmetric but structurally symmetric Holliday junction resulted. A marker in this region would show half conversion (segregate 5:3) if it were not mismatch-corrected. Diffusion-driven or enzyme-driven sliding of the junction away from the point of initiation would result in segments of reciprocal (symmetric) heteroduplex DNA. (In 1974, HOLLIDAY grafted sliding junctions onto his own model.) By appropriate adjustment of the

relative durations of the initial asymmetric phase and the subsequent symmetric phase, a wide range of fungal data could be embraced by the model. For yeast, the paucity of evidence for symmetric heteroduplex DNA was simply accounted for by supposing that the symmetric phase was vanishingly short relative to the asymmetric one. The relative shortage of 5:3 tetrads in yeast was accounted for by supposing that correction enzymes in yeast were more active than they are in other fungi.

Just as ROBIN's model had dominated the recombination field for a decade, CHARLEY and MATT's model ruled for the next decade. It is, of course, a mark of the importance of the Holliday model that it was replaced by evolution rather than by revolution, and both of HOLLIDAY's innovations, the junction and mismatch correction of heteroduplex DNA, retained central roles in the new model.

However, the Meselson-Radding model, in its turn, ran into troubles. Some of these troubles are easy to appreciate and will serve to introduce the next generation of models. In the Meselson-Radding model, in contrast to that of HOLLIDAY, one participating chromatid is identifiable as the aggressor and the other as the responder. [Asymmetry in the early steps of recombination had been postulated earlier by HOTCHKISS (1973), among others.] The mechanism proposed for recombination initiation, DNA synthesis in the chain displacement mode, results in a net gain of one (simplex) copy of information from the initiating chromatid with the loss of one simplex copy from the responder. This results in an incipient 5:3 tetrad, which can be mismatch-corrected to give a full conversion tetrad (6:2) or to restore the Mendelian ratio of 4:4.

In the Meselson-Radding model, the aggressor chromosome blows information into the responding chromosome. Studies on recombination-promoting sites in *Schizosaccharomyces pombe* (GUTZ 1971) and Neurospora (CATCHESIDE and ANGEL 1974) correctly foretold the behavior of all subsequently discovered "recombinator" sites by showing that, rather than blowing, these genetic elements suck information from the responding chromosome. This troubles the Meselson-Radding model. [RADDING (1982) later modified the model to fit this new fact.] A second finding troubling the Meselson-Radding model was the evidence from yeast that, when incipient 5:3 tetrads were acted upon by presumptive mismatch-correction enzymes, they were (almost) always converted to 6:2 tetrads. Somehow, within the framework of the model, the correction enzymes could identify the invading chain and effect correction in its favor (giving 6:2) rather than in favor of the invaded chromatid (restoring 4:4). That made some of us wonder whether correction really played a role in yeast conversion. If the symmetric phase is vanishingly short, and if correction is hyperactive, evidence for correction of a heteroduplex intermediate vanishes. Might not one

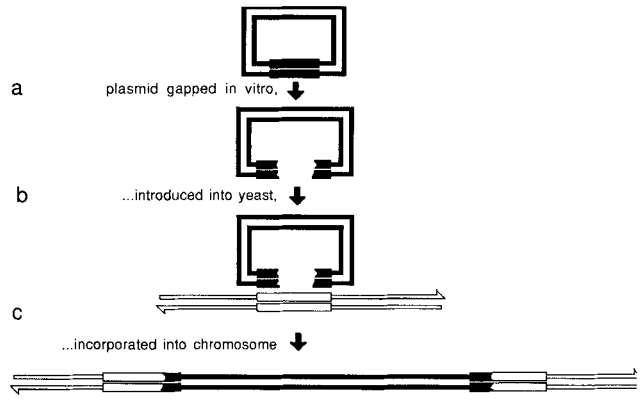

FIGURE 3.—Repair of a gapped plasmid (ORR-WEAVER *et al.* 1981). (a) A plasmid carrying a segment of yeast DNA was gapped within the yeast DNA by a restriction enzyme cut at the site of a deletion. (b) The gapped (linearized) plasmid was introduced into yeast cells, which were then plated under conditions that select for a different gene carried by the plasmid. (c) Since the plasmid could not replicate in yeast, all the selected transformants were a result of incorporation of the plasmid into the chromosome by homologous recombination between the gapped segment of yeast DNA and its undeleted wild-type homolog in the yeast chromosome. Plasmid incorporation was accompanied by repair of the gap, so that the plasmid was found flanked by two full, wild-type copies of the DNA segment.

chromatid simply donate two chains' worth of information directly to the other? One class of models based on this concept (STAHL 1969, 1979) was given little respect. Another, however, started a revolution.

In 1981, ORR-WEAVER *et al.* confirmed the observation of HICKS *et al.* (1979) that a double-chained break in a fragment of yeast DNA carried by a plasmid stimulated crossing over that incorporated the plasmid into the chromosome. The incorporated plasmid was flanked by a duplication of the region corresponding to the yeast fragment carried by the plasmid. These demonstrations of the recombinogenicity of a double-chained break confirmed, in an especially dramatic way, a conclusion reached earlier by RESNICK and MARTIN (1976) on the basis of X-ray stimulation of recombination in yeast. Especially significant in the revolution was the demonstration (ORR-WEAVER *et al.* 1981) that a sizable double-chained gap engineered into the region of homology stimulated incorporation of the plasmid into the chromosome and that both copies of the duplicated region were complete in the final product (Figure 3). This repair of a double-chained gap is equivalent to full conversion without mismatch correction–the information for repairing each of the chains is derived directly from the intact homolog. Furthermore, the aggressor element (the gapped plasmid) sucks information from the responding element (the intact host chromosome). This demonstration was just what seemed to be needed for meiotic recombination in yeast: full conversion without correction and aggressor chromosomes that sucked. The double-chain-break/gap-repair model for yeast

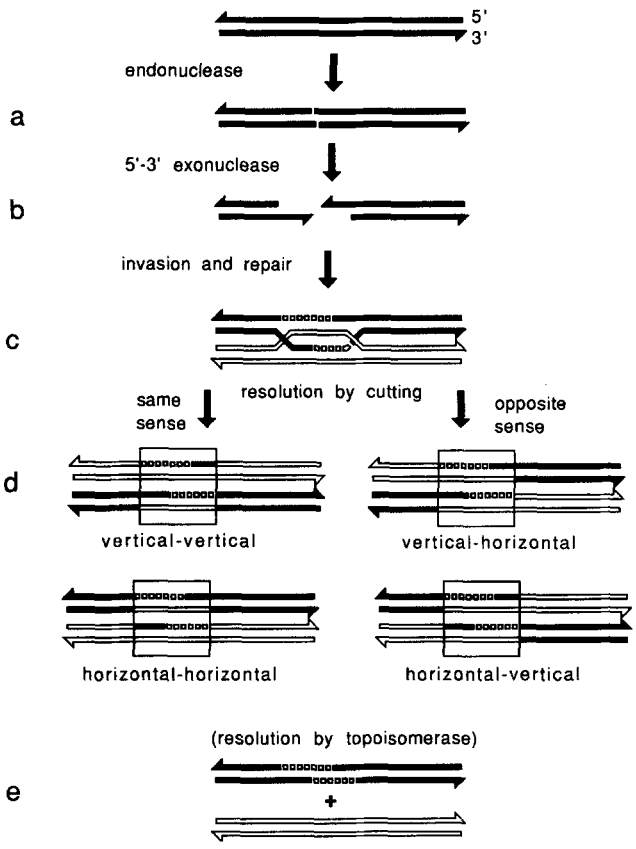

FIGURE 4.—The double-chain-break repair model. (a) A chromatid (or duplex) is cut on both chains, at an enzyme-accessible recombinator site. (b) Exonucleolytic digestion in the 5′ to 3′ direction exposes 3′ overhangs. These overhangs may sometimes be digested, too. (c) The 3′ ends invade the intact homolog. In yeast, sequence differences between the two participants may provoke further digestion of the 3′ overhangs. The 3′ ends prime DNA synthesis that replaces the DNA lost from the aggressor duplex. Ligation completes a four-chained intermediate in which duplexes are held together by a pair of Holliday junctions. (d) The junctions can be resolved either vertically or horizontally. When each is resolved in the same sense, no crossover results, but markers near the recombinator site will manifest either half or full conversion. When the junctions are resolved in the opposite sense, crossing over results, and the tetrad will again manifest conversion for markers near the recombinator site. The squares indicate the region between the two resolved junctions. In contrast to intermediates with one Holliday junction, the double Holliday junction structure of this model may be resolved without crossing over by the action of topoisomerase (THALER *et al.* 1987). This route is attractive for its unique ability to yield one pristine product.

soon followed and was published (SZOSTAK *et al.* 1983) after ORR-WEAVER and SZOSTAK (1983) confirmed an important prediction of the model, that about half the instances of plasmid repair occurred without incorporation of the plasmid into the chromosome. Thus, conversion by double-chain-gap repair modeled meiotic conversion in yeast in every important respect.

The double-chain-break/gap-repair model, too, made use of Holliday junctions (Figure 4). In this respect, it differed from the double-chain-break model offered earlier by RESNICK (1976). (Models without Holliday junctions have rarely made it to first base.)

Thus, HOLLIDAY's junction survived the revolution, embodied in a model that rejected most of the features of his model for recombination. (i) Initiation was no longer symmetric. (ii) Both chains of a duplex, rather than one chain, were cut to initiate recombination. (iii) Heteroduplex DNA was relegated to a minor role, and conversion occurred without a requirement for mismatch correction. This perspective put Saccharomyces outside the fungal pale, within which the Meselson-Radding model was doing very well (*e.g.*, HAMZA *et al.* 1981). Subsequent developments, described below, drew yeast and other fungi onto common ground.

The importance of double-chain breaks in the initiation of meiotic recombination in yeast was confirmed by the demonstration that meiotic initiators of recombination, whose presence was inferred by the gradients of gene conversion emanating from them, were sites for spontaneous meiosis-specific double-chain breaks (SUN *et al.* 1989; NICOLAS *et al.* 1989). Deletion of these break sites eliminated both the breaks and the high rates of recombination in their vicinity. Double-chain breaks were shown to be effective stimulators of recombination in *Escherichia coli* and phage, as well. However, the double-chain-gap repair version of the model was soon challenged. WILLIAMSON *et al.* (1985) isolated mutant yeasts in which aberrant 5:3's, normally rare for most markers in yeast, were as common as 6:2 tetrads. BISHOP *et al.* (1987) showed that these strains were deficient in mismatch-correction activity. The implication was clear—many of the 6:2 tetrads seen in wild-type yeast are the result of mismatch rectification of incipient 5:3 tetrads. Thus, in many instances, the initiating double-chain break (Figure 4) is not appreciably enlarged to a gap, so that much conversion is the result of heteroduplex DNA formation followed by correction. However, even the repair-deficient strains give appreciable numbers of 6:2 tetrads, and some of these may represent tetrads in which double-chain breaks were enlarged to double-chain gaps prior to interaction with the homolog.

If, as argued above, much conversion in yeast is the result of mismatch correction, how can we account for the apparent shortage of restorations, tetrads in which the heteroduplex is rectified so as to restore the 4:4 ratio of alleles? The very structure of the intermediate postulated in Figure 4 suggests the answer, which experiments by HABER *et al.* (1993) support. In the intermediate, the invading chains from the cut duplex are discontinuous for a time. Like the new, discontinuous chains at a replication fork, they could be recognized as targets for correction not by enzymes that replace a bit of mispaired chain but by the post-replicational repair system, which removes hundreds of bases from a growing chain. Thus, if the correction enzymes acted concurrently with intermediate formation, the invading

chain might be removed from its tip to beyond the mismatch. The break would thus be enlarged to a gap, and the genetic consequences of conversion by such mismatch correction would be difficult to distinguish from the predictions of the original double-chain-gap repair model of SZOSTAK *et al.* (1983).

Work by SCHWACHA and KLECKNER (1994) supports the notion of the four-chained intermediate flanked by Holliday junctions that was proposed by SZOSTAK *et al.* (1983). The former investigators isolated and examined a four-chained structure that arises at a prominent double-chain-break hot spot in yeast. The four single chains in each intermediate are parental for markers flanking the hot spot at some remove (SCHWACHA and KLECKNER 1994). Some of these same chains, however, are recombinant with respect to each of these flanking markers and to a marker located close to the break site, consistent with conversion accompanying repair of the double-chain break. Furthermore, exposure of the four-chained structures *in vitro* to a Holliday junction resolvase from *E. coli* converts them to an essentially equal mixture of duplexes (presumably nicked) that are parental and recombinant respectively for the flanking markers (A. SCHWACHA and N. KLECKNER, personal communication).

Note that the double-chain-break repair model (Figure 4) retains not only the Holliday structure but central features of the Meselson-Radding model, as well. (i) Thanks to the 3′ overhangs created at the break site (SUN *et al.* 1989, 1991), there is a region of asymmetric heteroduplex DNA (on each side of the break). (ii) Once a Holliday junction is formed, it may slide outwards, forming a region of symmetric heteroduplex DNA.

HOLLIDAY's junction has been a cornerstone of recombination models since its introduction. Consequently, it has been a focus for biochemical investigations, as well. The ability of junctions to slide, postulated by MESELSON (1972) and assumed in the Meselson-Radding model, was confirmed by *in vitro* studies on isolated structures (THOMPSON *et al.* 1976). Subsequent studies revealed enzymes in bacteria that promote such sliding (IWASAKI *et al.* 1992; WHITBY *et al.* 1993).

Enzymes capable of resolving Holliday junctions *in vitro* were sought and found in phage T4 (MIZUUCHI *et al.* 1982), in *E. coli* (DUNDERDALE *et al.* 1991; IWASAKI *et al.* 1991), and elsewhere. Mutants lacking these enzymes are frequently recombination deficient.

MAX DELBRÜCK presented HOLLIDAY's recombination model at a meeting at Lake Arrowhead. MAX liked much of the model but objected that mismatch correction, if it operated by removing a mispaired bit of chain, would prevent the construction of intragenic linkage maps. MAX scorned a suggestion that the relevant correction enzymes might remove stretches of DNA of appreciable and variable length, preserving intragenic mapability. [HOLLIDAY (1964) dealt with mapability by proposing marker-dependent pairing problems.] MAX dictated against the invention of an enzyme just because genetic phenomenology called for it. He was wrong again–a major mismatch-correction system does remove long, variable stretches of DNA. My goodness, even the oocyte of the African clawed toad has such a system (LEHMAN *et al.* 1994). Furthermore, the history of recombination studies is replete with the discovery of enzymes that were previously posited just to make the models work.

So, just which ideas from HOLLIDAY's (1964) model are retained in the reigning double-chain-break/gap model? (i) The junction is there (except now there are two of them). (ii) Mismatch correction of heteroduplex DNA contributes to conversion (except that now there is an additional contribution to the conversion process in terms of mismatch-independent generation of 3′ overhangs and the subsequent replacement of the DNA lost in that reaction, and, perhaps, DNA from both chains may sometimes be lost independently of any mismatches, so that the entire conversion occurs without mismatch correction). That's an impressive record, really. ROBIN's model was the lightning rod for 30 years of research, and its central assumptions, though modified, have survived every strike. Congratulations, ROBIN!

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