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Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

Unequal Crossing Over Then and Now

THE *Bar* eye mutation of Drosophila occupies a rather special place in the history of genetics. As the experiments of STURTEVANT and MORGAN (1923) and STURTEVANT (1925) showed, it was the first example of unequal crossing over and also the first demonstration of position effect. Over the past 65 years our understanding of position effects has remained largely unresolved, but our knowledge and appreciation of the importance of unequal crossing over has grown substantially. While much remains to be learned, I think it is now clear that the phenomenon of unequal recombination is a matter of considerable significance for genetic biology. It is, therefore, the subject of this *Perspectives* on the occasion of the 65th anniversary of its discovery.

I am going to focus on two basic modes by which unequal crossing over occurs. One involves direct tandem redundancy, whereas the other is mediated by transposons. My purpose is to illustrate these two situations with examples from diverse organisms in order to provide a sense of the context in which they occur and to understand the questions they raise. Because our concept of unequal crossing over derives directly from studies of the *Bar* mutation, it is useful to consider these in some detail.

Bar is a dominant, homozygous viable, sex-linked mutation that reduces, in heterozygotes, the number of facets in the compound eye to about half their usual value. By 1921 ZELENY had shown that *Bar* was unstable and could mutate at considerable frequency (6×10^{-4}) to either wild type or to a more severe phenotype he referred to as *ultra Bar*. However, no mechanism to explain this anomalous behavior seemed obvious until STURTEVANT and MORGAN (1923) reported the results of a disarmingly simple experiment. They marked chromosomes carrying *Bar* (*B*, 57.0 cM) with the flanking mutations *forked* (*f*, 56.5 cM) and *fused* (*fu*, 59.5 cM) to produce $f^+ B\ fu/f\ B\ fu^+$ heterozygotes and found that the Bar^+ revertant progeny were also recombinant for the adjacent markers, being either $f^+ fu^+$ or $f fu$. Their conclusion was unequivocal: "... reversion of *Bar* to normal is associated with crossing over at or near the *Bar* locus."

But the matter was not to rest there. Two years later, in 1925, STURTEVANT solved the riddle of the unusual properties of *Bar* in a publication entitled "The effects of unequal crossing over at the Bar locus in Drosophila." It is a remarkable paper. At the outset, STURTEVANT advances the hypothesis that both the *ultra Bar* mutants and the wild-type revertants arise from $f^+ B\ fu^+/f\ B\ fu$ individuals by unequal crossing over at *Bar*. He proposed that if the site of recombination lies to the left of *Bar* in one chromosome, but to the right of it on the other, then the *ultra Bar* mutants should be more properly referred to as *double Bar* because they would be genotypically $f\ BB\ fu^+$ or $f^+\ BB\ fu$ and, hence, duplicated for *Bar*. The wild-type revertants, on the other hand, would be $f^+ fu$ or $f\ fu^+$ and deficient for *Bar*. Accordingly, *double Bar* and wild-type revertants are necessarily reciprocal products of the same exchange event and should be recovered in equal numbers. In fact, they are not. This is probably due to the reduced viability of *double Bar* and the difficulty of distinguishing it from *Bar* alone. However, what made the unequal crossing over hypothesis so compelling was STURTEVANT's discovery and use of a new allele of *Bar* known as *Bar-infrabar* (B^i). This mutation arose spontaneously in a *Bar* stock and reduces the number of eye facets to a value intermediate between *B* and wild type and thereby made it possible to devise a crucial test of the unequal crossing over mechanism. STURTEVANT was able to derive, for example, the tandem arrangement of BB^i from B/B^i heterozygotes and then to recover separately the *B* and B^i alleles in their proper order with respect to flanking markers.

It would be 11 years, until the discovery of polytene chromosomes, before STURTEVANT's unequal crossing over hypothesis could be confirmed. MULLER, PROKOFIEVA-BELGOVSKAYA and KOSSIKOV (1936) and BRIDGES (1936) found that the *Bar* mutation itself is a direct tandem duplication of seven bands that compose section 16A1-7 of the polytene map. Unequal crossing over results when the distal repeat of one chromosome recombines with the proximal repeat in the opposite homolog to yield Bar^+ revertants and

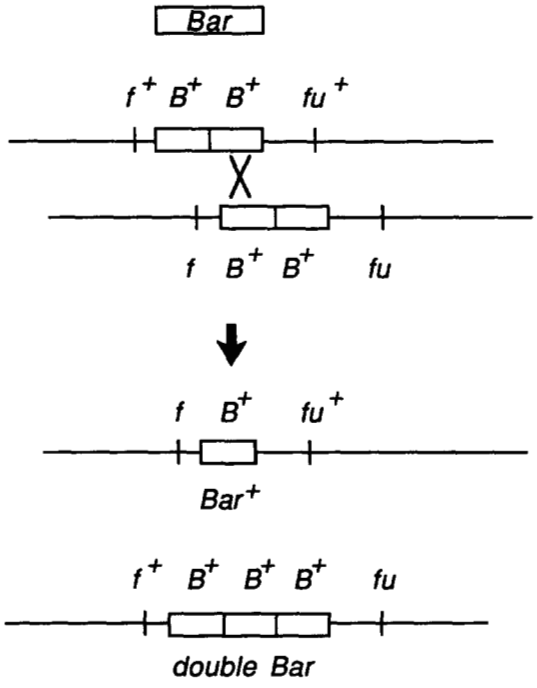

FIGURE 1.—Unequal crossing over at *Bar*. The large open rectangle at the top represents the *Bar* tandem duplication whereas each smaller rectangle below denotes one copy of the Bar^+ (B^+) locus which spans section 16A1-7 on the polytene map. One of two possible misalignments of the *Bar* duplication is illustrated. In this case, unequal exchange in $f^+ B\ fu^+/f\ B\ fu$ heterozygotes produces $f\ B^+\ fu^+$ (Bar^+) and $f^+\ BB\ fu$ (*double Bar*) progeny that possess one and three copies of the Bar^+ locus, respectively. Recently, STUART TSUBOTA (personal communication) has observed the presence of a 7.5-kb transposon inserted at the 16A7-16A1 breakpoint in the middle of the *Bar* duplication. This suggests that the duplication itself may have been formed in the process of transposon mobilization.

double Bar progeny (Figure 1). Thus, the reversion of *Bar* does not involve a loss of the *Bar* locus as initially thought, but rather a loss of the duplicate copy of section 16A; conversely, *double Bar* actually contains three doses of the Bar^+ region.

Since recombination was known to take place at the four-strand stage, STURTEVANT considered the possibility that unequal sister chromatid exchange might be responsible for some of the changes in *Bar*. However, after examining more than 36,000 offspring from homozygous *B* or B^i females, every instance of either reversion or augmentation of *Bar* was also accompanied by crossing over between *f* and *fu*. If unequal sister chromatid exchange ever occurs here, it is a rather rare event. Nevertheless, PETERSON and LAUGHNAN (1963) pursued the issue further in an elegant series of experiments. They searched for exceptional nonrecombinant B^+ male offspring produced from females that were either: (1) hemizygotes, carrying *f B fu* on one *X* chromosome and a deficiency for *Bar* on the other; (2) heterozygotes, bearing *f B os* on one *X* (*os*, outstretched small eye, 59.2 cM), and the other an inversion containing $f^+\ B\ os^+$; or finally (3), heterozygotes of the genotype $f\ B\ os/f^+\ B\ os^+$. In total, they obtained 9 nonrecombinant *B* to B^+ revertant males among 215,376 progeny for a frequency of about 4×10^{-5}. This value is 15 times lower than the comparable interchromatid event which they found to be 6×10^{-4} (46 recombinant revertants among 78,433 progeny).

Similarly, JACKSON and FINK (1985) have shown that in Saccharomyces the occurrence of unequal sister chromatid exchange between two copies of a direct tandem duplication of the *HIS4* gene is also 10–20-fold less frequent than the comparable rate of interchromosomal recombination. Although the cause of this striking suppression of intrachromatid unequal exchange in both flies and yeast is unknown, it does suggest the presence of a well regulated pathway controlling these events. JACKSON and FINK have proposed that suppressing sister chromatid crossing over might be selectively advantageous by reducing the production of deficiencies and inversions that would otherwise result from intrastrand exchange between direct or inverted repeats on the same chromosome. This speculation may be particularly relevant to micro-repeats, sequences 2–10 bp in length and separated from each other by less than 1 kb, that participate in the generation of spontaneous deletions through illegitimate exchange as previously discussed in these *Perspectives* by ANDERSON (1987).

In contrast to the situation for unique genes like *Bar* and *HIS4*, highly redundant sequences such as the ribosomal RNA genes (rDNA) have a propensity for unequal sister chromatid exchange. RITOSSA *et al.* (1966) showed that in Drosophila there is a 100–200 copy array of these genes imbedded within the centric heterochromatin of the *X* chromosome and another on the short arm of the *Y* and that partial deficiencies of rDNA result in a short-bristle phenotype known as *bobbed* (*bb*). He subsequently made the remarkable discovery that when *X* chromosome *bb* mutants are maintained for several generations with a *Y* chromosome deficient for most of its rDNA (Ybb^-), as in bb/Ybb^- males, phenotypically bb^+ flies containing a wild-type amount of rDNA appear (RITOSSA 1968). This phenomenon has been referred to as "magnification."

In order to explain the very existence of *bobbed* mutants, RITOSSA *et al.* (1966) speculated that they might arise by unequal crossing over. However, the possibility that unequal exchange was responsible for magnification was rejected by both RITOSSA (1968, 1972, 1973) and ATWOOD (1969). Part of the difficulty in understanding this phenomenon was that it occurred only in males, a gender in which meiotic recombination is virtually absent. However, as a result of examining the frequency of magnification in single males rather than in populations of flies, I proposed that the mechanism by which magnification occurs is unequal mitotic sister chromatid exchange (TARTOF 1974). I demonstrated that rDNA magnification arises

primarily in mitotically active germ cells and at a frequency such that 80% of the offspring of some *bb/Ybb*$^-$ individuals are *bb*$^{m+}$ (magnified wild type *bb*$^+$). This frequency of magnification is several orders of magnitude higher than expected for interchromosomal meiotic recombination events. Moreover, the *Ybb*$^-$ chromosome not only induces rDNA magnification of *bb* mutants but is also able to decrease the rDNA content of the wild-type *bb*$^+$ locus, a phenomenon referred to as "reduction." It was further shown that magnification and reduction are reciprocal events in *bb/Ybb*$^-$ germ cells, although *bb*$^{m+}$ progeny are recovered more frequently than their reduction-produced lethal counterparts (*bb*^{rlethal}). This might be expected owing to selection against *bb*^{rlethal} germ cells in a manner reminiscent of the under-representation of *double Bar* recombinants observed by STURTEVANT. Finally, magnification of a *bb* mutation when present in a ring *X* chromosome is diminished as might be expected because single (or odd-number) crossovers are lost as double-size dicentric chromosomes. More recently, we have shown that under nonselective conditions, recovery of *bb*$^{m+}$ and *bb*^{rlethal} products is equal and that, although the vast majority of the magnified *bb*$^+$ progeny from *bb/Ybb*$^-$ males arise premeiotically, some of these magnifying events also occur at meiosis (HAWLEY and TARTOF 1985).

There are two genetic factors crucial to the process of ribosomal gene magnification and reduction. First, the presence of the *Ybb*$^-$ chromosome is required. What makes this chromosome so mutagenic is not clear. It is deficient for most of its own rDNA, but this alone does not explain its behavior because *Ybb*$^-$ chromosomes have been constructed with a wild-type rDNA content and they are still effective at inducing magnification (HAWLEY and TARTOF 1983). However, it may be that *Ybb*$^-$ is deficient for a critical pairing site and this leads to misalignment between the rDNA clusters when homologous regions of the *X* and *Y* synapse. Second, some of the genes (*mei-41, mus-101, mus-108*) that control meiotic recombination and DNA repair are also required for magnification-reduction, whereas others (*mei-9, mus-102, mus-109*) are not (HAWLEY and TARTOF 1983; HAWLEY *et al.* 1985). It is interesting to note that those genes affecting rDNA magnification and reduction are also involved in post-replication repair.

Just as the rDNA of Drosophila may undergo unequal sister chromatid exchange in both mitotic and meiotic cells, similar events occur in Saccharomyces. By virtue of site-specific transformation, it has been possible to insert a single *LEU2* gene into the tandemly arrayed rDNA cluster located on chromosome *XII* of yeast. Measurement of the frequency of increase and decrease in *LEU2* copy number has provided an unequivocal genetic and molecular demonstration of the regular occurrence of unequal sister strand exchange within the rDNA cluster of mitotic cells (SZOSTAK and WU 1980) as well as meiotic cells (PETES 1980). In mitotic cells, about 10^{-2} unequal sister chromatid exchange event is observed per generation. In meiotic cells, the frequency of unequal sister strand exchange is at least 10^{-1} per meiosis, while recombination between nonsister chromatids is suppressed.

A somewhat similar situation has also been observed in the mouse. The distal ends of mammalian *X* and *Y* chromosomes frequently pair and undergo reciprocal exchange in gametogenesis. As a consequence, the pattern of inheritance of markers located in this region is not strictly sex-linked and is called pseudoautosomal. HARBERS *et al.* (1986) have isolated a mouse containing a single Moloney murine leukemia virus (M-MuLV) genome inserted in the pseudoautosomal region of the *Y*. The M-MuLV proviral sequence is readily transferred from the *Y* to the *X* and back again at a frequency of about 10^{-1}. Moreover, approximately 7% of the offspring from males homozygous for M-MuLV (X^{Mov}/Y^{Mov}) contain either no provirus or two copies of it. Since the proviral insert is flanked by a tandemly redundant sequence (repeat length ~1.3 kb), a plausible explanation for the gain and loss of proviral DNA is unequal crossing over between the repeated elements. It is not known if some of these events are premeiotic or involve sister chromatids. Such issues may be resolved, both in this case and in mammalian systems in general, by using restriction fragment length polymorphisms (RFLPs) as chromosome markers flanking the site of unequal exchange to determine precisely the source of alteration in gene copy number.

In humans, too, there is evidence for unequal crossing over. JEFFREYS, WILSON and THEIN (1985) have described a probe that detects hypervariable, dispersed, tandemly redundant "minisatellite" regions whose repeat lengths vary from 16 to 64 bp and are highly polymorphic in the human genome. In fact, these repeat lengths are so polymorphic from one person to the next that they provide a means for detecting individual-specific DNA. The likely source of such polymorphism is unequal crossing over. In an incisively direct experiment, JEFFREYS *et al.* (1988) examined human pedigrees with five different minisatellite probes to determine the rate at which new alleles (DNA restriction fragments) appear. For each individual probe, the mutation rate per gamete varied from undetectable to as high as 5×10^{-2} for the most unstable locus.

The examples of unequal crossing over at *Bar*, in rDNA, in the pseudoautosomal region of the mouse and in the minisatellites of humans all share a common structural feature: direct tandem repetition of genetic sequence. It is conceptually straightforward to understand how unequal crossing over among repeated sequences arises when there are two or more identical

sites, and hence, substantial opportunity for misalignment between the iterated copies. But what causes unequal crossing over in genetically unique portions of the genome where tandem duplication is not apparent? What sort of homology is required, and how extensive must it be, to effect asymmetric exchange?

Considerable progress toward answering these questions has been provided by GOLDBERG *et al.* (1983) and DAVIS, SHEN and JUDD (1987). They examined the molecular structure of reciprocal duplications and deficiencies produced by interchromosomal unequal exchange in Drosophila females heterozygous for various *white* (*w*) alleles. In the experiments of GOLDBERG *et al.* it was found that a 7.2-kb transposable element (*BEL*) was present in both w^a and w^{a4} mutants but inserted at slightly different locations in each mutant, about 60 kb apart and in the same orientation. Further analysis demonstrated that asymmetric pairing and exchange between the staggered *BEL* sequences are responsible for the observed duplications and deficiencies. The frequency of unequal exchange between these two *white* alleles is about 2×10^{-4}. DAVIS, SHEN and JUDD examined unequal crossing over in w^{ric}/w^{bf} heterozygotes. w^{ric} possesses an 8.7-kb *roo* transposon located at 0 kb on the molecular map of *white* whereas w^{bf} contains two *roo* elements, one at −1.1 kb and the other at +31.9 kb. All three *roo* inserts are oriented in the same direction. Here, too, unequal crossing over is transposon-mediated. In w^{ric}/w^{bf} heterozygotes the frequency of unequal exchange between the *roo* elements at 0 and −1.1 is four times higher (2×10^{-4}) than between the *roo* transposons located at 0 and +31.9 (5×10^{-5}). This indicates that the interaction between transposons may be inversely related to the distance that separates them.

What is perhaps most astonishing about these results is that small (8-kb) displaced regions of homology, in the form of transposons, are able to pair with each other at considerable frequency despite separation by 60 kb and despite being surrounded by extensive regions of standard homology. At present, we do not understand how transposons participate in this process. Anecdotal observations (BURKE JUDD, personal communication) indicate that the heterozygosity of transposon locations may be important because w^{bf} homozygotes, with their two *roo* elements only 33 kb apart, seem to show no evidence of asymmetric exchange. This would suggest a mechanism of transposon-mediated unequal crossing over whereby homolog pairing in heterozygotes results in looped-out unpaired transposons that recombine with each other in a distance-dependent manner. Still, the extent to which heterozygosity affects this process needs to be clearly defined. It is also possible that a transposase is involved. The genes that control transposon-mediated unequal exchange are yet to be identified. In this regard it would be useful to examine the effect of overexpression of the appropriate transposase as well as the impact that various recombination and DNA repair mutations might have on transposon-mediated unequal crossing over.

Because small, slightly displaced transposons appear to be such a significant feature of unequal crossing over, the question arises of how many times per genome one might expect members of the same transposon family to be sufficiently close (for instance, within 60 kb) to pair with each other and undergo unequal exchange. In *Drosophila melanogaster* there are about 70 different mobile element families, each represented on average about 33 times in the euchromatic portion of the genome (YOUNG 1979). Given these parameters, SAM LITWIN and I have calculated, by both analytical means (LITWIN 1974) and by computer simulation, the frequency distribution of two identical transposons located on the same chromosome arm and displaced by ≤60 kb. Assuming all transposons to be randomly distributed, our results predict about 13 instances per Drosophila genome, similar to the w^a/w^{a4} situation where two members of the same transposon family reside within 60 kb or less of each other and in the same orientation. It follows, then, that the average genomic frequency of transposon-mediated unequal crossing over per meiosis in Drosophila might be $(2 \times 10^{-4}) \times 13$ or about 3×10^{-3}. This is a very high rate for a mutagenic process.

Since the frequency of unequal exchange is so high and so ubiquitous, it is not surprising to observe its impact on human disease. Either tandem duplications (as in *Bar*) or transposons (as in w^a/w^{a4}) may be involved.

Color blindness, an *X*-linked disease that affects about 8% of Caucasian males, in an example of unequal crossing over mediated by gene duplication. This locus codes for the red and green visual pigment apoproteins and is organized as a head-to-tail tandem array composed of a single red-pigment gene at the 5′ end followed by a variable number (one, two or three) of green-pigment genes (NATHANS, THOMAS and HOGNESS 1986; VOLLRATH, NATHANS and DAVIS 1988). The polymorphism for the number of green-pigment genes is probably explained by unequal crossing over. Examination of genomic DNA from males with two different forms of color blindness revealed the presence of an interesting pattern of rearrangements (NATHANS *et al.* 1986). One class of color blindness, anomalous trichromacy, has been thought to result from the presence of photopigment with an altered absorption spectrum. In fact, analysis of the DNA from such individuals demonstrates the presence of either a 5′ red—3′ green or a 5′ green—3′ red hybrid photopigment gene. These data are most easily explained by unequal crossing over between red-pigment and green-pigment loci. This seems likely given the fact that their DNA sequences

are 98% identical and that the number of green-pigment genes is so variable. In a second type of color blindness, referred to as dichromacy, the red or green photopigment is missing as a consequence of either gene deletion or red-green gene fusion. Here, too, the mutations can be most easily explained by unequal crossing over, although gene conversion may sometimes occur. Similarly, hemoglobinopathies, such as certain α-thalassemias, hemoglobin Lepore and hemoglobin Kenya, illustrate the concept of unequal exchange between tandemly related loci (for a review see COLLINS and WEISSMAN 1984).

Perhaps the clearest human example of unequal crossing over involving displaced transposons comes from studies of familial hypercholesterolemia. This malady is a consequence of a defect in the gene coding for the LDL (low density lipoprotein) receptor, a transmembrane glycoprotein responsible for the binding of LDL and its eventual endocytosis in coated pits. LEHRMAN *et al.* (1987a,b) have described a duplication and a deletion mutation that appear to result from unequal crossing over between Alu sequences located in different introns of the locus.

From the foregoing discussion is is apparent that the eukaryotic genome is constantly expanding and contracting in size. Results from Drosophila indicate that, for the genetically unique portion of the genome, transposon-mediated unequal exchange may result in duplications or deficiencies of at least 60 kb or so once in every 300 meioses. This will have special consequences for wild-type genes whose phenotypes are sensitive to dosage. In Drosophila, dosage-sensitive loci include *Bar*, the *bithorax* complex, *runt, Notch, Enhancer-Suppressor of Hairless,* modifiers of *Polycomb, Minutes,* and *Enhancer-Suppressors of variegation*. For the repetitous component of the genome, evidence from Drosophila, yeast, mice and humans indicates that the frequency of unequal crossing over per meiosis is on the order of 10^{-1} for some sequences. While it has been suggested that continual unequal exchange provides a means for maintaining the homogeneity of tandemly repeated sequences (SMITH 1973), other processes such as gene conversion may be as important, if not more so, in this regard (JACKSON and FINK 1981; KLEIN and PETES 1981).

In the context of evolution, new proteins are derived from older ones by gene duplication. Proteins, particularly those with extracellular function such as the LDL receptor, the serum albumin family and the epidermal growth factor family, are often built up from a smaller unit of amino acid sequence that is then reiterated as a tandem array. The duplication of an entire gene, or portions of its internal structure, may be considered simply a consequence of unequal crossing over where the exchange event requires regions of homology either in the form of multiple gene copies or interspersed transposons. Thus, the pathologic manifestations of duplication and deletion mutations as they occur in the human LDL receptor are but a reflection of the mechanism by which the gene itself was created. It might be reasonably argued that as the number of gene copies or transposons increases, so should the rate of unequal exchange. But unequal crossing over is a mutagenic event that would be expected to have negative, often lethal consequences as a result of altering gene dosage or producing novel gene fusions. Thus, the tendency to constantly accumulate gene duplications may be limited by the adverse impact these extra DNA sequences usually have. Likewise, increases in transposon copy number may also be constrained by their potential for deleterious effects through unequal exchange (LANGLEY *et al.* 1988).

We know embarrassingly little about the role unequal crossing over plays in the genetic life of somatic cells. Even in Drosophila, where it should be possible to obtain some information on the frequency of this process, there are few compelling facts. However, malignant cells by their very nature clonally amplify rare genetic events and therefore provide a useful source of biological material with which to investigate this problem. An interesting example in this regard concerns the homogeneously staining regions (HSRs) of mammalian chromosomes that are found only in tumor and drug-resistant cells. They represent a form of gene amplification which evidence suggests is a product of unequal sister chromatid exchange (HOLDEN *et al.* 1987). Although direct evidence is lacking, unequal crossing over may also be one of the several means by which potentially malignant cells establish homozygosity or hemizygosity for somatically recessive cancer genes (KNUDSON 1971).

In his book *A History of Genetics,* STURTEVANT (1965) modestly regarded the *Bar* eye case as ". . . too special to serve as a basis for any general picture of mutation. . . ." Indeed, it is a special paradigm, but not in the restrictive sense. I suspect STURTEVANT would be pleased with the broad and general importance of his contribution, and how things are turning out.

KENNETH D. TARTOF
Institute for Cancer Research
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, Pennsylvania 19111

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