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DOBZHANSKY, BATESON, and the Genetics of Speciation

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That essential bit of evolutionary theory which is concerned with the origin and nature of *species* remains utterly mysterious. W. BATESON (1922)

SIXTY years ago, THEODOSIUS DOBZHANSKY (1936) took a large step towards solving "the Species Problem." He published his seminal work on the genetics of speciation in these pages, an analysis of hybrid sterility between two sibling species, *Drosophila pseudoobscura* (then called "race A") and *D. persimilis* ("race B"). This work is renowned among evolutionary geneticists for several reasons. Most important, DOBZHANSKY showed that the genetics of species differences—even reproductive isolation itself—could be studied with the same genetic tools that had been wielded so successfully *within* species. In doing so, he was quickly able to put several popular theories of speciation to the sword. (Indeed, some of these hypotheses were so thoroughly dispatched that their very existence is now forgotten.) DOBZHANSKY's paper also lent strong support to an alternative view of speciation that he and H. J. MULLER are usually credited with introducing. This view—that hybrid sterility and inviability are caused by sets of interacting "complementary genes"—laid the foundation for nearly all subsequent work in the genetics of speciation, including the recent explosion of papers in this journal.

Despite the fact that DARWIN left the species problem largely unsolved (see below), geneticists made few forays into speciation before the 1930s. There were two reasons for this neglect. For one thing, there was simply too much else to do in the early years of Mendelism: mutants had to be mapped and chromosome mechanics untangled. But speciation also posed serious technical problems. The study of, say, hybrid sterility was invariably foiled by the very phenotype under study; sterile flies do not, after all, afford the most promising material for genetics. This simple problem had stopped dead in its tracks the only previous serious venture into speciation, STURTEVANT's (1920) work on *D. melanogaster–D. simulans* hybrids. All of the hybrids were sterile or inviable, and little could be done.

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But all this changed in 1922. In that year, DONALD LANCEFIELD, working in MORGAN's lab at Columbia, found a stock of what was then called *D. obscura* that produced sterile males when crossed to all other stocks. But the hybrid females (and this was the important part) remained fertile. With LANCEFIELD's discovery of what came to be called *D. persimilis* (the new stock) and *D. pseudoobscura* (the old stocks), the door swung open on the genetic study of speciation. Here were beasts that both thrived in Drosophilists' vials and that yielded sterile hybrids *and* some fertile hybrids upon crossing.

But as PROVINE (1981) recounts in his careful history of this period, DOBZHANSKY grew frustrated by LANCEFIELD's slow progress. A long ten years after LANCEFIELD's initial discovery, DOBZHANSKY had had enough and announced his intent to start his own work on *D. pseudoobscura.* DOBZHANSKY published several brief reports on hybrid sterility in 1933 and 1934, but he dropped the bomb in his 1936 paper, a work that was far more complete and far more convincing than any preceding it.

DOBZHANSKY's approach was simple enough. In a forerunner to quantitative trait locus (QTL) analysis, he crossed *D. pseudoobscura* carrying mapped visible markers (one to three per chromosome) to *D. persimilis.* By backcrossing the fertile F_1 females to males from either of the pure species, he recovered backcross hybrids carrying many combinations of chromosomes from the two species. By scoring the fertility of these hybrids, which he assessed by measuring testis size, DOBZHANSKY could see which chromosome regions, if any, caused hybrid sterility. As LEWONTIN (1981) has rightly emphasized, here, finally, was a study of speciation that looked a good deal like genetic studies within species: crosses were made, balancer chromosomes were used, and *XO* males were characterized, all on material that was by then cytologically well known.

The nucleus *vs.* the cytoplasm: DOBZHANSKY's greatest finding is today the most easily overlooked: hybrid sterility is caused by genes. This fact was far from obvious in the 1930s. Debate over the cause of hybrid sterility had raged for decades and, as always, vague specula-

tion proliferated in inverse proportion to the number of experiments. Although lumping these speculations is tricky, several did share a common theme: species differences, it was claimed, are not caused by Mendelian genes. Instead, something unique, some novel process or novel kind of factor, causes speciation and the differences seen among species. This reluctance to render unto MENDEL what (it turned out) was clearly MENDEL's appeared in two forms, one saner than the other.

First, a surprisingly large number of biologists held that, while Mendelism might explain the trivial and uninteresting differences seen within species, Morganist genes could never explain species differences. These "fundamental" or specific differences were instead due to the cytoplasm. This view was especially popular among European embryologists (*e.g.*, LOEB and BRACHET), but even luminaries like JOHANNSEN (1923) claimed that "the Problem of [the Evolution of Species] does not seem to be approached seriously through Mendelism." Although members of this "cytocentric" camp were mostly concerned with morphological species differences, there was a strong suspicion that Mendelian genes could not explain *any* sort of difference between species. Indeed, SAPP (1987) argues that the well known failure of breeders to produce "good" species drove many biologists to the cytocentric view, for as HUXLEY and BATESON had emphasized, breeders had succeeded in duplicating virtually every evolutionary phenomenon *except* good species that produced sterile hybrids.

Second (and, to modern ears, more reasonably), many geneticists asserted that hybrid sterility resulted not from ordinary changes in ordinary genes, but from large chromosome rearrangements. These rearrangements allegedly disrupted chromosome pairing in hybrids, derailing meiosis. This view gained support from two lines of evidence: chromosome pairing problems clearly *were* the frequent cause of sterility in plants and, more important, meiotic chromosomes failed to pair in some sterile animal hybrids.

DOBZHANSKY's work falsified both the cytoplasmic and the rearrangement hypotheses. As he noted elsewhere, the "cytocentric" view was absurdly vague anyway: "It was only said that the latter [variation within races or species] is clearly genic, while the former [differences between races or species] was alleged to be non-Mendelian and to be due to some vague principle which assiduously escapes all attempts to define it more clearly" (DOBZHANSKY 1937a). Arguing that "the mechanisms isolating species from each other must be considered the only true specific differences, if the expression 'specific character' is to have any real meaning," DOBZHANSKY (1937a) set out to determine if reproductive isolation itself was Mendelian. His results were unambiguous.

Sterility of *D. pseudoobscura-D. persimilis* hybrids mapped to chromosomes. In backcrosses to *D. pseudoobscura*, for example, males carrying all three *X*-linked markers from *D. persimilis* were often sterile, while those carrying all three markers from *D. pseudoobscura* were almost always fertile. The effect was large and unquestionable. Moreover, recombination analysis showed that factors causing sterility resided on both the left and right arms of *X*. Similar results recurred at all the chromosomes: most of DOBZHANSKY's markers were associated with hybrid sterility. Any lingering hope for a fundamental role of the cytoplasm (maybe the chromosomes and the cytoplasm together cause hybrid sterility?) were shattered by DOBZHANSKY's next result: "Backcross males having only race A chromosomes are fertile irrespective of whether they have the cytoplasm derived from race A or from race B. Backcross males having only race B chromosomes are likewise fertile irrespective of the source of their cytoplasm." Ironically, DOBZHANSKY found that the fertility of one hybrid genotype did vary with its cytoplasm, but he quickly showed that this was due to a maternal effect (depending on the mother's nuclear genotype), not to some autonomous force lurking in the cytoplasm. In sum, "no indication . . . of an inherent difference between the cytoplasms of the two races is apparent" (DOBZHANSKY 1936, p. 126) (although we do now know that intracellular endosymbionts such as Wolbachia sometimes cause hybrid lethality, though not sterility, in insects.) Two years later, in a review entitled "The nature of interspecific differences," J. B. S. HALDANE (1938) announced that Mendelian genes also explained *morphological* differences between species, and the cytocentric hypothesis sank into well-deserved obscurity.

Genes *vs.* chromosome rearrangements: Although this "sterility is due to chromosomes" result was anticipated by the previous work of LANCEFIELD (1929) and KOLLER (1932) (indeed, DOBZHANSKY barely found the cytoplasmic hypothesis worthy of mention by 1936), DOBZHANSKY's paper went far beyond its predecessors. DOBZHANSKY showed not only that hybrid sterility is due to chromosomes, but that this effect is in turn due to genes, not to large rearrangements. Although *D. pseudoobscura* and *D. persimilis* differed by six inversions and although meiotic chromosomes failed to pair in hybrids, several lines of evidence proved that the rearrangements were not to blame. For one thing, four of the inversion differences were *X*-linked and so could play no role in hybrid *male* sterility. DOBZHANSKY (1936) further showed that hybrid sterility often mapped to regions that were *not* heterozygous for rearrangments in hybrid males, *e.g.*, both arms of the *X* and the fourth chromosome. Indeed the *X*-linked factors had the largest effect on hybrid fertility.

Last, DOBZHANSKY had previously shown that structural differences between species did not even cause the pairing problems seen in hybrids, much less sterility *per se*. DARLINGTON (1932) had earlier discovered a remarkable pattern proving that hybrid sterility in plants involves chromosome rearrangement: while diploid hy-

brids often display univalents at meiosis and are sterile, tetraploid hybrids between the same species display bivalents and are fertile. Because all chromosomes have perfect pairing partners in tetraploid hybrids, the simple availability of unrearranged partners clearly rescues fertility. DOBZHANSKY (1933), in what, for my money, stands among the cleverest experiments in evolutionary genetics, showed that DARLINGTON's rule is *not* obeyed in animals. Sidestepping the fact that one can't make tetraploid males, DOBZHANSKY compared the frequency of pairing failure in diploid *vs.* tetraploid hybrid *spermatocytes* (tetraploid cells being fairly common in *D. pseudoobscura–D. persimilis* hybrid testes). Remarkably, he found that chromosomes fail to pair just as often in tetraploid cells, where all chromosomes have perfect pairing partners, as in diploid cells. Hybrid meiotic problems were not due to structural incompatibilities.

DOBZHANSKY would drive the message home in his book, *Genetics and the Origin of Species* (1937b): while hybrid sterility in plants is often due to chromosome rearrangements, hybrid sterility in animals is not. Although exceptions surely occur here and there, this conclusion has been largely confirmed in the recent burst of work on the genetics of speciation in Drosophila: hybrid sterility typically maps to genes.

Complementary genes: DOBZHANSKY's 1936 paper is best remembered for yet another reason: it provided the best evidence yet that speciation occurred by what is now called the "DOBZHANSKY-MULLER" model. It is hard to overestimate the importance of this simple model. Indeed, it resolved a paradox that had stared down evolutionists for half a century: how could something as patently maladaptive as the evolution of sterility or inviability be allowed by natural selection? Although DARWIN obviously did not subscribe to the modern biological species concept, he was painfully aware of the problem posed by hybrid sterility. He recognized that he asked his readers to believe both that most evolution is due to natural selection and that sterility of hybrids routinely evolves. Indeed, DARWIN spent an entire chapter of the *Origin of Species* trying to explain away this paradox, but his attempt was less than overwhelmingly successful. Hence the common (and correct) charge that the *Origin of Species* neglected to explain the origin of species.

To see DARWIN's paradox, consider the simplest possible scenario: a single gene causes hybrid sterility. One species has genotype *AA* and the other *aa*. While each species is fertile, *Aa* hybrids are sterile. Now consider how these species could evolve from a common ancestor, say, *AA*. They can't. Starting with two allopatric *AA* populations, one simply remains *AA* while the other must become *aa*. But how can it? The *a* mutation, like any mutation, has the unfortunate property of arising in the heterozygous state. But the resulting *Aa* individual *is* the sterile hybrid genotype, and the line comes crashing to an end.

DOBZHANSKY's solution was simple. Hybrid sterility, he said, involves an interaction between at least *two* genes. To see this, let our allopatric populations begin with an *aabb* genotype. An *A* mutation appears and gets fixed in one population; the *Aabb* and *AAbb* genotypes are perfectly fertile. Indeed *A* may be selectively favored. A *B* mutation appears and gets fixed in the other population; the *aaBb* and *aaBB* genotypes are also fertile. And, again, *B* may be favored. The critical point is that, although *B* is compatible with *a*, it hasn't been "tested" with *A*. We simply have no guarantee that *A* and *B* can work together. Indeed, *AaBb* hybrids may be sterile. The point is deceptively simple: if hybrid sterility is caused by epistatic incompatibilities *between* loci, Darwin's paradox is resolved. Speciation can occur and two taxa can become separated by an adaptive valley even though *no genotype ever passed through the valley.*

This model is very simple. In fact, it has proved too simple for many evolutionary biologists, who have offered countless elaborate ways of getting populations across adaptive valleys, explaining speciation. (We evolutionists have a long track record of preferring fancy over simple theories, dating from our infamous reluctance to surrender GALTON in the face of Mendelism. Surely something as *déclassé* as 3:1 ratios were not to be preferred to GALTON's sophisticated and seductive mathematics.) Alas, the simple theory has once again proved right. Although geneticists dissecting the basis of postzygotic isolation continue to squabble over many details, we *all* agree that hybrid sterility and inviability in animals is caused by sets of complementary genes (WU and BECKENBACH 1983; COYNE 1992; ORR 1995).

DOBZHANSKY's paper provided the clearest evidence yet for this new model of speciation. DOBZHANSKY beautifully showed not only that the *X* from *D. persimilis* and the second chromosome from *D. pseudoobscura* caused hybrid sterility, but that sterility resulted from an *interaction* between these (and other) chromosomes, and hence between different loci. Evolutionists were no longer free to imagine that hybrid sterility was typically caused by heterozygote disadvantage or by inversions and translocations (although many continued to do so, *e.g.,* KING 1993).

DOBZHANSKY was not the first to find complementary incompatibilities in hybrids. Several hybrid complementary systems were known by the 1930s (BELLAMY 1922; HOLLINGSHEAD 1930). DOBZHANSKY gets credit because he, unlike his peers, saw that complementary sterility was more than a technical curiosity: he saw that, unlike single-gene sterility, two-gene sterility resolved DARWIN's paradox. DOBZHANSKY first hinted at this idea in an absurdly obscure paper in 1934, noting that, while the distinction between complementary *vs.* single genes isn't important as far as the physiology of sterility is concerned, it is "obviously important as far as the way of the establishment of the genetic differences of this kind in a wild population is concerned" (DOBZHANSKY

1934). This is (uncharacteristically modest) code-talk for "complementary genes can explain the origin of species." DOBZHANSKY again hinted at this message on the first page of his 1936 paper and finally spelled it out in his book, where the model is laid out step by step with some fanfare. In the end, then, DOBZHANSKY's title was considerably less misleading than Darwin's: *Genetics and the Origin of Species* really did explain the origin of species.

BATESON's forgotten role: While DOBZHANSKY seemed content to present the gist of the complementary gene model, H. J. MULLER gave it its most careful treatment. MULLER (1940, 1942) considered the evolution of hybrid sterility in two classic papers. His 1942 essay, "Isolating mechanisms, evolution, and temperature," is an especially remarkable and insightful work. (The odd title reflects the fact that the paper was delivered at a session ostensibly devoted to temperature; MULLER insisted on speaking about speciation instead and his paper makes only a few strained references to temperature.) In this paper, MULLER offered a number of important refinements of the complementary model.

He showed that complementary lethals and steriles could evolve between species even when all substitutions occurred in one lineage (a fact that is still often misunderstood). He showed that, in Drosophila, complementary incompatibilities are often "complex," involving interactions between triplets, etc., not pairs, of genes. He speculated on the biochemical basis of hybrid incompatibilities: do hybrid problems involve genes that act as poisons or as loss-of-function alleles on a "foreign" genetic background? And, most important, he considered *X* linkage and offered an explanation of HALDANE's rule (the preferential sterility or inviability of the hybrid *XY* sex) which, in slightly modified form, could well be right (TURELLI and ORR 1995).

DOBZHANSKY and MULLER's views of the complementary model differed subtly (*e.g.,* MULLER's emphasis on "transfer of function"). Consequently, each later tended to preferentially cite his own formulation of the idea. As it turns out, their concern with precedent was utterly beside the point: I recently discovered that WILLIAM BATESON offered the "DOBZHANSKY-MULLER" model in 1909, just nine years after the rediscovery of Mendelism and a good quarter-century before DOBZHANSKY or MULLER. And when I say that BATESON offered the model, I do not mean that he obliquely alluded to it. Rather, BATESON spells it out, step by step, presenting it as the likely "secret of interracial sterility" (BATESON 1909).

BATESON's 1909 discussion appears in a forgotten essay, "Heredity and variation in modern lights," in an equally forgotten volume, *Darwin and Modern Science.* (To appreciate how long ago BATESON's essay appeared, consider that its preface was penned by DARWIN's longtime associate, J. D. HOOKER.) Midway through his essay, BATESON asks what discovery would most advance our understanding of evolution, and concludes that he'd most like to see hybrid sterility laid bare. After all, as noted above, hybrid sterility remained the sole evolutionary phenomenon not duplicated among artificially selected varieties.

BATESON's explanation of how sterility could evolve between varieties is identical to that later offered by DOBZHANSKY and MULLER. He first notes that "when two species, both perfectly fertile severally, produce on crossing a sterile progeny, there is a presumption that the sterility is due to the development in the hybrid of some substance which can be formed only by the meeting of two complementary factors." He then explains, in a remarkably prescient passage, how such factors evolve (p. 98, italics in original):

> Now if the sterility of the cross-bred be really the consequence of the meeting of two complementary factors, we see that the phenomenon could only be produced among the divergent offspring of one species by the acquisition of at least *two* new factors; for if the acquisition of a single factor caused sterility the line would then end. Moreover each factor must be separately acquired by distinct individuals, for if both were present together, the possessors would by hypothesis be sterile. And in order to imitate the case of species each of these factors must be acquired by distinct breeds. The factors need not, and probably would not, produce any other perceptible effects . . . Not till the cross was actually made between the two complementary individuals would either factor come into play, and the effects even then might be unobserved until an attempt was made to breed from the cross-bred.

BATESON even proposes a way of testing his conjecture. Noting that the pair of factors causing sterility between two closely related varieties might not yet be fixed in either line, he suggests obtaining "a pair of parents [one from each breed] which are known to have had any sterile offspring, and to find the proportions in which these steriles are produced. If, as I anticipate, these proportions are found to be definite, the rest is simple." In short, he expects such crosses will show that sterility is due to Mendelizing factors and, further, to *pairs* of interacting factors: "My conjecture therefore is that in the case of sterility of cross-breds we see the effect produced by a complementary pair of such factors." Although BATESON stumbles in a few places (*e.g.,* he thinks his model explains hybrid sterility but not hybrid inviability), he clearly foresaw the simple "secret of interracial sterility." Why, then, has his role been forgotten?

The chief reason is that neither DOBZHANSKY nor MULLER acknowledged BATESON's precedent. (They, of course, occasionally cite BATESON, but, as far as I can tell, never this essay, and never for this idea.) There are good reasons for thinking neither DOBZHANSKY nor MULLER knew of BATESON's model. For one thing, BATESON unveiled his model in a less-than-visible place, although his essay was reprinted in 1928 in *William Bateson, Naturalist,* a posthumous collection. More im-

portant, BATESON apparently never repeated his argument. While my search has not been exhaustive, BATESON does not offer his model in his more popular writings, even when discussing speciation. In *Problems of Genetics* (1913), his most widely read work, BATESON devotes his entire last chapter to hybrid sterility. While he suggests that hybrid sterility results from "complementary factors" (p. 238), he never explains why this is important nor how such factors can evolve. Indeed, the book ends with a depressing confession that once-confident evolutionists "no longer see how varieties give rise to species." By 1922, BATESON was reduced to admitting that "When students of other sciences ask us what is now currently believed about the origin of species we have no clear answer to give. Faith has given place to agnosticism." [And there is no doubt that by "species" BATESON more or less meant biological species: the "chief attribute of species [is] that the product of their crosses is frequently sterile" (BATESON 1922).] Two years before his death, BATESON lamented that "no general principles governing the incidence of interspecific sterility have been ascertained" and thus that "of the origin of specific distinctions we have . . . no acceptable account" (BATESON 1924). BATESON, to put it mildly, suffered a few doubts about his earlier solution to DARWIN's "mystery of mysteries." Indeed, as the years wore on, he grew increasingly obsessed and depressed by Darwinism's failure to crack the Species Problem which, to BATESON, meant the origin of hybrid sterility.

There is, of course, one other reason why DOBZHANSKY and MULLER may not have known of BATESON's precedent. BATESON, as the most vocal champion of Mendelism, harbored deep reservations about natural selection. To DOBZHANSKY and MULLER, BATESON surely represented an ancient (and somewhat unfriendly) regime that was irredeemably confused about evolution. BATESON was, to some extent, one of the enemies battled against during the modern synthesis. The inevitable lack of communication between the Mendelian old-guard and the modern synthetic upstarts probably had something to do with DOBZHANSKY and MULLER's oversight. Indeed, only HALDANE seems to have followed BATESON's evolutionary work (see especially HALDANE 1958, his fond assessment of BATESON).

By recalling BATESON's precedent in a commemoration of DOBZHANSKY's 1936 paper, it may seem that I give to DOBZHANSKY with one hand while taking away with the other. But this is not my intent. It is, after all, one of the virtues of science that those who differ on larger issues, as BATESON and DOBZHANSKY surely did, can nonetheless arrive at the same conclusion. Recent work on speciation renders this coincidence all the happier: for BATESON and DOBZHANSKY not only arrived at the same conclusion, but at the right conclusion.

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