Synthetic Lethals: A Critical Review

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Received 21 January 1986; 29 May 1986

Abstract: Synthetic lethality results from epistatic (non-additive) interlocus interactions. Synthetic lethal combinations have been found among the recombinant products of non-lethal chromosomes as well as among existing lethals. Synthetic lethals have also been found among newly arising lethal mutations, among laboratory mutant combinations, and in crosses involving different races and species. Despite their drastic phenotypic effect, they are difficult to detect. Work on recombinational synthetic lethals has suffered from inadequate controls for spontaneous mutation, and mapping experiments are often insufficient to distinguish synthetic lethals from single-locus lethal effects. Though synthetic lethals appear to be relatively rare, the data are inconclusive and synthetic lethal systems with closely linked components could be common. It appears that a disproportionately large number of temperature sensitive lethals are also synthetic. There are hints that aspects of fitness other than viability may be subject to large epistatic interactions.

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1. Introduction

Most characteristics of evolutionary interest are influenced by many loci. This raises an important problem. Do such characteristics reflect the cumulative independent contributions of each locus, or do the loci interact "non-additively" or epistatically, so that their combined effect is more than a simple blend of individual contributions? Questions concerning the nature and magnitude of epistatic fitness effects have profound implications for evolutionary genetics. For example, the consequences of sexual reproduction (Thompson, 1976), the nature of speciation events (Carson and Templeton, 1984), and the nature of genetic load (Seager and Ayala, 1982) all depend on the nature of interlocus fitness interactions, and Wright's influential shifting balance model of evolution is based on the assumption that such interactions commonly occur (Wade and McCauley, 1984).

Though there is abundant evidence for epistatic fitness interactions, there is no consensus concerning how important such interactions are in the evolution of natural populations (see reviews by Lewontin, 1974; Hedrick et al., 1978; Barker, 1979). Some geneticists have emphasized the role of interlocus interactions and consequent genetic coadaptation while others have emphasized the independent evolution of alleles at different loci (Felsenstein, 1975).

Synthetic lethality (Dobzhansky, 1946) is an extreme epistatic fitness effect in which the interaction of otherwise harmless genes produces death. The concept of synthetic lethality epitomizes an interactionist approach to the multilocus determination of fitness, while the concept of lethal equivalents (Morton et al., 1956), in which death stems from the additive deleterious effects of alleles at two or more loci, epitomizes a noninteractionist approach to the same phenomenon. Historically, evidence concerning synthetic lethals played a significant role in the debate between the "classical" and "balance" schools of population genetics (see, for example, the exchange between Dobzhansky, 1964a, 1964b, and Crow, 1964). Below I review the evidence for synthetic lethals. Though most of the work in question concerns Drosophila, I have also included a few examples from other organisms.

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Evolutionary Theory 8: 1-13 (October, 1986)
The editors thank C.B. Krimbas and another referee for help in evaluating this paper.

2. Recombinational Synthetic Lethals

Dobzhansky (1946) first reported synthetic lethal chromosomes among the recombination products of a pair of Drosophila pseudoobscura chromosomes. Both parental chromosomes were homozygously viable at 16°C but three out of fifty-three recombinant chromosomes proved to be lethal at the same temperature. Dobzhansky also found three semilethals (with relative viabilities in the range 15-30%) among thirty-three recombination products of another pair of homozygously viable chromosomes. He attributed these newly arisen deleterious effects to the interaction of individually harmless chromosome segments brought together by recombination and coined the termssynthetic lethal and synthetic semilethal to describe them. For practical purposes we can define a synthetic lethal as a genotypic combination conferring a relative viability of less than 10% and owing its deleterious effect to strong epistatic interactions among its constituent parts.

Misro (1949) repeated Dobzhansky's work using D. melanogaster and found that compared to male and female controls, heterozygous females produced a higher frequency of lethal second chromosomes. He attributed the excess lethals to synthetic lethality. Later, Wallace et al. (1953), Hildreth (1955, 1956) and Gantner (1958) made larger scale attempts to demonstrate the generation of recombinational synthetic lethals in D. melanogaster. The results were not definitive (Table 1). About the same time, Dobzhansky and several collaborators launched a coordinated attempt to assess the contribution of recombination to genetic variation in five Drosophila species. The results, which include extensive data on synthetic lethality, were published in a numbered series titled "Release of genetic variability through recombination".

In four species (D. pseudoobscura, D. persimilis, D. prosaltans and D. willistoni) the frequency of lethal chromosomes recovered was rather high (2.4% to 5.7%), suggesting that some newly arising lethals might be synthetic rather than mutational in origin (Table 1). However, the absence of adequate controls for spontaneous mutation to lethality makes interpretation difficult. For example, Spassky et al. (1958), working with D. pseudoobscura, tested only 120 "recombinant" chromosomes from homozygous females to control for spontaneous mutation and were forced to rely on a later mapping experiment (Dobzhansky and Spassky, 1960) for firm evidence of synthetic lethals. In the whole series of experiments only Spiess and Allen (1961) carried out a full scale set of controls, using heterozygous males. Like Hildreth and Gantner before them and Allen (1966) in a later experiment, they found no difference in the frequency of lethals among recombinant and non-recombinant D. melanogaster chromosomes.

Even the use of male controls is clouded by uncertainty because it relies on the assumption that male and female lethal mutation rates are the same, an assumption that has never been adequately tested. Though male and female mutation rates appear to be equal in D. melanogaster X chromosomes (Woodruff et al., 1983), the data for autosomes are limited and in the largest relevant experiments with wild-derived flies Wallace (1968, 1970) measured consistently (though not significantly) higher female mutation rates in D. melanogaster X, second and third chromosomes. Interestingly, the excess female-derived lethals are attributable to clusters occurring among the recombinant chromosomes of certain females. Wallace suggests that these clusters reflect premeiotic mutation but, with the exception of one set of experiments in which he used females heterozygous for the recombination suppressing Basc chromosome, they could also reflect the recurrent generation of synthetic lethals from particular chromosome pairs.

Assuming male and female mutation rates to be equal and taking heterozygous males as controls, we can use data from three large experiments (Misro, 1949; Wallace, 1968; Kosuda and Moriwaki, 1971) to estimate the rate of formation of second chromosome synthetic lethals in D. melanogaster. Under this assumption, between 0.2% and 1.6% of the recombinant chromosomes carry a newly arising synthetic lethal and between 26% and 78% of all newly arising lethals are synthetic. However, in two out of these three cases the marked excess of lethals among female derived chromosomes is statistically insignificant, despite the large number of chromosomes tested. This highlights a prob-

Table 1. A SUMMARY OF WORK ON RECOMBINATIONAL SYNTHETIC LETHALS IN DROSOPHILA.

Report	Species[a]	Chromosome[b]	No. leth./No. tested Recombined	No. leth./No. tested Controls[c]	Synthetics present?[d]
1. Dobzhansky '46	pseu	2nd(3)[e]	3/159	none	?[g]
2. Misro '49, Wigan '49	mel	2nd(3)	25/1204	3/667 m 4/641 f	yes[g]
3. Wallace et al. '53					
Intrapopulation	..	2nd(10)	87/2079	7/581 f	yes
Interpopulation	..	.. (10)	56/2751		
4. Hildreth '55	..	X(10)	13/5186	1/994 f	no
5. Hildreth '56	..	3rd(8)[h]	15/2771	18/2693 m	no
6. Gantner '58	..	2nd(8)[h]	13/3063	4/598 m 1/372 f	no
7. Spassky et al. '58					
Intrapopulation	pseu	2nd(20)	44/900	0/120 f	yes[g]
Interpopulation	..	.. (20)	33/1000		
8. Spiess '58 & '59					
Intrapopulation	per	2nd(20)	19/900	none	?
Interpopulation	..	.. (20)	26/1000		
9. Dobzhansky et al. '59					
Intrapopulation	pro	2nd(20)	45/900	none	?
Interpopulation	..	.. (20)	64/1000		
10. Krimbas '61	wil	2nd(10)	21/450	none	?
11. Spiess & Allen '61	mel	2nd(10)	2/450	1/450 m	no
	..	3rd(10)	2/450	2/450 m	
12. Allen '66	..	2nd(6)	2/150	3/150 m	no
	..	3rd(6)[i]	4/150	1/150 m	
13. Mukai & Yamazaki '68	..	2nd(4)[j]	0/106	0/98 m	no
14. Wallace '68	..	2nd(-)[j]	20/2337	22/3454 m	?
	..	3rd(-)[j]	22/3067	16/2797 m	
15. Batten & Thoday '69	..	2nd(29)[h]	56/3553	none	yes[g]
16. Wallace '70	..	X(-)[j]	42/13489	33/13605 m	?
17. Kosuda & Moriwaki '71	..	2nd(63)	75/2071	13/530 m	?
18. Gallo '81[k]	..	X(4)	1/138	none	?
19. Martins & Mourao '81[k]	..	X(-)[j]	1/560	none	?

[a] pseu=pseudoobscura, mel=melanogaster, per=persimilis, pro=prosaltans, wil=willistoni.
[b] Number of separate chromosomes recombined in parentheses.
[c] Nature of controls: m=heterozygous males, f=homozygous (isogenic) females.
[d] Present author's interpretation, which in some cases differs from that of the original author(s): yes=positive statistical or other evidence for synthetic lethals, no=lack of evidence for synthetic lethals, ?=absence of controls or marked but statistically insignificant excess of lethals among recombinant chromosomes.
[e] Recombined chromosomes included one temperature sensitive lethal.
[g] Includes mapping evidence.
[h] Each recombining chromosome pair included one multiple marker chromosome.
[i] Recombined two pairs of chromosomes that had been allowed to accumulate mildly deleterious mutations over many generations.
[j] Undefined number of chromosomes recombined.
[k] Investigation confined to sex-limited female lethals.

lem inherent in synthetic lethal detection programs that require the measurement of background spontaneous mutation rates. Unless the number of chromosomes tested is very large, on the order of many tens of thousands, even substantial rates of generation of synthetic lethals will go undetected. In the absence of a very large full factorial experiment comparing the rates of lethal formation in heterozygous and homozygous males and heterozygous and homozygous females, these surprisingly high estimates carry little weight.

On balance, the evidence for recombinational synthetic lethals is weak. It rests primarily on statistical comparisons of very low power, reflecting the intrinsically low rate of appearance of new lethals and the difficulty of testing more than a few thousand chromosomes in a single set of experiments. In many cases, even disregarding problems of scale, adequate controls have not been performed.

3. Bichromosomal Synthetic Lethals

While hard evidence for recombinational synthetic lethals has proven to be elusive, we can turn our sights around and ask what proportion of naturally occurring lethal effects are synthetic (Lewontin, 1974). Study of interchromosomal interactions provides the simplest approach. In some Drosophila species non-homologous chromosomes can be simultaneously extracted from individual flies. When the single homozygotes for each chromosome exhibit normal or near normal viability but the double homozygotes die, lethality is synthetic. Several experiments of this kind have been performed, in all but one case with the second and third chromosomes of Drosophila melanogaster (Table 2).

In the most extensive survey, Temin et al. (1969) found nine putative bichromosomal synthetic lethals among nine hundred fifty D. melanogaster lethal combinations, but not all of these cases could be confirmed on retesting. Other examples of bichromosomal synthetic lethals are few and far between and some represent artificial combinations of chromosome pairs derived from different flies or different populations. These "artificial" bichromosomal synthetic lethals are formally analogous to the recombinational synthetic lethals discussed above. Apparently, bichromosomal synthetic lethals are not common in natural populations.

The methodology used to detect bichromosomal synthetic lethals also reveals cases in which homozygosity for one chromosome "cures" or represses lethality caused by homozygosity for another chromosome. Such bichromosomal "cured" lethality (Seager and Ayala, 1982), a special case of bichromosomal synthetic lethality, has been reported on at least three occasions (Table 2) but also appears to be rare.

In the experiments cited in Table 2 average epistatic viability effects were small, suggesting that the rarity of interchromosomal synthetic lethals reflects an absence of consistent large interchromosomal epistatic effects. Recently, however, Seager et al. (1982) investigated interchromosomal epistatic effects using a broader measure of fitness, competitive success in population cages. They found that while homozygosity for a single D. melanogaster autosome drastically reduces fitness, homozygosity for two autosomes is, on average, no worse than homozygosity for one. In a few cases double homozygotes were substantially fitter than either single homozygote, a situation analogous to cured lethality in the viability studies (so many of the single homozygotes had relative fitnesses of less than 10% that analogies to synthetic lethality are not useful). This suggests that while interchromosomal synthetic lethals are rare, other strong interchromosomal epistatic fitness effects could be common (more on this below).

4. Intrachromosomal Synthetic Lethals

If crossing over between homologous chromosomes creates synthetic lethals, it should be possible to recombinationally desynthesize a portion of existing single chromosome lethals. Lethal effects that can be mapped to single loci or broken down

TABLE 2. A SUMMARY OF WORK ON BICHROMOSOMAL SYNTHETIC LETHALS IN *DROSOPHILA*.[a]

Report	No. tested combinations (no. lethal)	Number synthetic lethals	Number cured lethals
1. Matsudaira '63[b]	58(23)	0	1[c]
2. Dobzhansky et al. '65	120(?)	2[d]	1[d]
3. Wallace et al. '66	119(89)	0[e]	0
4. Temin et al. '69	1855(950)	9[f]	0
5. Tsuno '70			
Cage population	125(36)	2[d]	0
Natural population	86(37)	2[d]	1[d]
6. Kosuda '71			
Natural combinations	166(0)	0	-
Artificial combinations[g]	101(2)	2	-
7. Seager & Ayala '82	154(84)	0	1
8. Miyashita & Laurie-Ahlberg '84[g]	100(1)	1[h]	-

[a] With the exception of Dobzhansky et al. (1965), who studied 2nd and 3rd chromosome combinations in *D. pseudoobscura*, each case concerns 2nd and 3rd chromosome combinations in *D. melanogaster*.
[b] All combinations tested were derived from a single, irradiated, initially isogenic line.
[c] Asserted to be an artefact produced by a 2nd-3rd chromosome translocation.
[d] Ambiguous case.
[e] Found three apparently non-epistatic "combination lethals".
[f] Some of these could not be confirmed on retesting.
[g] Artificial combinations of non-lethal chromosomes from same population.
[h] Of seven possible cases reported only one proved to be a synthetic lethal (Miyashita, personal communication).

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into additive deleterious components are not synthetic. But, lethal chromosomes that can be decomposed into two or more harmless segments must be synthetic lethals. Dobzhansky and Spassky (1960) and Batten and Thoday (1969) have confirmed the existence of a few newly arising recombinational lethals using this approach.

Ives (1945) performed the first desynthesis of a natural lethal. He mapped fifty-six *D. melanogaster* second chromosome lethals and found one due to double homozygosity for visible mutations at loosely linked loci. Gibson and Thoday (1962) have described a dominant second chromosome synthetic lethal combination in the same species. More recently, Thompson (in press) screened forty-two *D. melanogaster* second chromosome lethals for interarm synthetic lethality. One proved to be synthetic. Breese and Mather (1960), Kenyon (1967), Mourad et al. (1980), Bishop et al. (1981) and Begon et al. (1984) also report synthetic lethals in *D. melanogaster* but present no evidence (and Kenyon, 1972, has apparently retracted her claim). On the other hand, Spiess et al. (1963) report no clearcut synthetic lethality among several suspect second and third chromosome lethals in *D. melanogaster*, and neither Watanabe and Oshima (1966) nor Paik (1960) report evidence for synthetic lethality in mapping experiments on one hundred thirty-five *D. melanogaster* second chromosome lethals. In other species, Magalhães and his colleagues (1965a, 1965b) describe a high frequency synthetic lethal system in *D. willistoni* and Sperlich and Feuerbach-Mravlag (1974) report a dominant synthetic lethal inversion combination in *D. subobscura*.

Overall, the desynthesis experiments demonstrate that natural synthetic lethals occur but suggest that cases involving loosely linked components are relatively rare. However, mapping and desynthesis experiments probably fail to detect a substantial fraction of intrachromosomal synthetic lethals. For example, closely linked synthetic

lethal combinations will segregate as Mendelian units operationally indistinguishable from single-locus lethals. Moreover, strongly interacting polymorphic loci may often be closely linked, both because selection generally favors reduced recombination between interacting loci (Smith, 1978) and because close linkage may favor the maintenance of epistatic polymorphisms (Charlesworth and Charlesworth, 1975a). If so, the most interesting and abundant synthetic lethals may be precisely those that are hardest to detect. Even if a synthetic lethal's components are not closely linked, it will generally evade detection so long as the components do not span a tester chromosome marker locus.

Making matters worse, mapping experiments reveal synthetic lethality only when the tester chromosome does not contain components of the lethal. To use Thoday's (1963) example, if ab is a recessive synthetic lethal combination and the multiply marked tester chromosome is of genotype Ab, then the synthetic lethal will map at the "A" locus in the standard mapping cross ab/Ab X Ab/Ab. Wallace (1981, p. 534) illustrates the same point for two, three and four-component synthetic lethals. Conversely, if a newly arisen single-locus lethal depends on the genetic background in which it arises for its lethality, it will prove to be synthetic on outcrossing to a tester stock of different background genotype (see below). Synthetic lethality is a slippery phenomenon. Given the inherent methodological difficulties, it is not surprising that reports of synthetic lethals are few and far between.

5. Mutational Synthetic Lethals

If the lethality of a newly arisen lethal mutation depends on the genetic background in which it occurs, the lethal effect is synthetic, even though the mutation itself involves only a single locus. Interestingly, mutational synthetic lethals appear to be relatively common among newly arising temperature sensitive mutations. Suzuki et al. (1967) report one experiment in which six of sixty-nine temperature sensitive D. melanogaster X-linked recessive lethal mutations were apparently synthetic. In subsequent experiments a number of other newly arising temperature sensitive lethals proved to be synthetic (Suzuki and Procunier, 1969; Mayoh and Suzuki, 1973). Parkash (1969) also reports a newly arising temperature sensitive synthetic lethal.

Temperature sensitivity has also been reported in association with several other cases of synthetic lethality. One of the D. pseudoobscura chromosomes giving rise to Dobzhansky's (1946) original synthetic lethals was itself a temperature sensitive lethal and Rizki (1955) has reported an apparent temperature sensitive synthetic lethal in D. willistoni. A recombinational synthetic lethal found by Thompson (in press) in D. melanogaster and several laboratory mutant synthetic lethal combinations (Table 3) also exhibit temperature sensitivity.

Though synthetic lethality appears to be rare among other classes of newly arising lethal mutations, a few possible cases have been reported. For example, Zimmering and Muller (1961) report a sex-limited D. melanogaster lethal expressed only in the presence of particular X, second and third chromosomes. In maize, Mangelsdorf (1974, pp. 108-109) notes that newly arising sugary endosperm alleles are virtually lethal in unselected genetic backgrounds. Evidently sweetcorns represent the horticultural desynthesis of synthetic lethal combinations.

6. Laboratory Mutant Synthetic Lethals

In addition to the "natural" synthetic lethal systems described above, investigators have described several lethal interactions involving laboratory mutations (Table 3). Many of these interactions involve eye pigment mutations (Lucchesi, 1968) or alleles of the forth chromosome eyeless locus. The Zw^{+}/Pgd^{-} synthetic lethal combination is notable as the only system for which the biochemical basis of synthetic lethality has been established. Homozygosity or hemizygosity for 6-phosphogluconate dehydrogenase (6PGD) null alleles (Pdg^{-}) is ordinarily lethal, but simultaneous homozygosity for glucose-6-phosphate dehydrogenase (G6PD) null alleles (Zw^{-}) restores viability

TABLE 3. LABORATORY MUTANT SYNTHETIC LETHAL COMBINATIONS IN DROSOPHILA MELANOGASTER.

Combination		Map position of loci		Reference
1. Dl,	M	3-66.2,	many	Schultz '29
2. pr,	ey_D	2-54.5,	4-2.0	Clemente '41[a]
3. D,	ey^D	3-40.7,	4-2.0	Sobels et al. '51[b,c]
4. pn,	K-pn	X-0.8,	3-102.9	Sturtevant '56
5. Ax,	H^6	X-3.0,	3-69.5	House '59[b]
6. Hn^{t3},	ry^6	3-23.0,	3-52.0	Goldberg et al. '62[d]
7. dor,	ry	X-0.15,	3-52.0	Lucchesi '68[e,f]
8. pd,	Pdr	2-106.4,	3-46	Lindsley & Grell '68
9. lt,	stw	2-55.0,	2-55.1	Lindsley & Grell '68
10. eyg,	ey	3-35.5,	4-2.0	Hunt '70
11. dor,	car	X-0.15,	X-62.5	Nash '71
12. car,	lt_D	X-62.5,	2-55.0	Nickla & Brown '73
13. Ax,	ci^D	X-3.0,	4-0.0	House & Lutes '75[b]
14. Pgd^-,	Zw^+	X-0.9,	X-63	Gvozdev et al. '77, Hughes & Lucchesi '77
15. cin^3,	v	X-0.0,	X-33.0	Bentley & Williamson '82[g]
16. M(3)S37h,	$M(3)h^y$	3-40.2,	3-40.2	Moscoso & Ripoll '83[h]
16. $para^{ts1}$,	nap^{ts}	X-53.9,	2-56.2	Ganetzky '84
17. $Sxl^{f\#1}$,	mle(3)132	X-19.2,	3-25.8	Uenoyama '84

[a] Green (1955) could not repeat this observation.
[b] Lethality temperature sensitive.
[c] Kidwell (1964) reports a synthetic lethal system involving ey^D and undetermined loci on other chromosomes.
[d] Thompson (1983) could not repeat this observation.
[e] Lethal interaction does not hold for all dor alleles (Bischoff and Lucchesi, 1971).
[f] Lucchesi also reports that dor cn bn and dor pd are near-lethal.
[g] Lethality dependent upon presence of dietary allopurinol.
[h] Though formerly attributed to a single locus at map position 3-40.2, these alleles belong to distinct loci lying some distance apart.

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(Gvozdev et al., 1977; Hughes and Lucchesi, 1977). While the cases in Table 3 are limited to D. melanogaster, a synthetic lethal mutant interaction has also been reported in Tribolium castaneum (Sokoloff, 1964) and such interactions no doubt occur in other species as well. These systems may prove useful in experiments designed to model the evolutionary dynamics of interacting genes.

7. Complementary Lethals

Sometimes crosses between distinct varieties of a single species result in the death of the offspring, apparently through the formation of lethal double heterozygotes (though phenomena like hybrid dysgenesis might also play a role). Such dominant complementary lethal effects have been described in rice (Chu and Oka, 1972; Sato and Hayashi, 1983), barley (Weibe, 1934), and wheat (Caldwell and Compton, 1943). Similar phenomena occur in interspecific crosses. When D. melanogaster and D. simulans are crossed, the male or female offspring ordinarily die as larvae (the sex depending on the direction of the cross), but offspring of both sexes survive when the D. simulans parent carries the lethal hybrid rescue allele (Watanabe, 1979). Likewise, offspring of the plants Crepis tectorum and Crepis capillaris die when the C. tectorum parent carries a specific lethal factor but live when the factor is absent (Hollingshead, 1930). Dominant complementary synthetic lethal systems are of special evolutionary in-

terest because they suggest a genetic basis for speciation (see Bengtsson and Christiansen, 1983, for discussion and mathematical analysis).

Interest in recessive complementary lethal effects stems from studies of the evolutionary consequences of gene duplication. When a vital locus is duplicated, both new loci may become polymorphic for null (inactive) alleles. Single null homozygotes live, but double null homozygotes die, leading to a simple synthetic lethal system. Several workers have modeled the dynamics of such systems, concentrating on factors influencing the rate of silencing of duplicate loci through fixation of null alleles (Fisher, 1935; Nei and Roychoudhury, 1973; Bailey et al., 1978; Kimura and King, 1979; Takahata and Maruyama, 1979; Allendorf, 1979; Li, 1980; Pritchett-Ewing, 1981; Maruyama and Takahata, 1981). Along with more general work by Christiansen and Frydenberg (1977) and Bengtsson and Christiansen (1983), these studies provide a quantitative theory of simple synthetic lethal systems.

8. Synthetic Sterility and Heterozygous Viability

While most studies of epistatic fitness interactions have focused on egg-to-adult viability, there is a small body of work concerning other components of fitness. Krimbas (1960) and Thompson (In press), for example, report apparent cases of recombinational synthetic sterility in D. willistoni and D. melanogaster, Kidwell (1969) describes a triple chromosome synthetic sterile combination in D. melanogaster, and Casady et al. (1960) report a dominant complementary synthetic sterile combination in sorghum. Of more general importance, Seager et al. (1982) have reported strong interchromosomal epistatic interactions for population cage fitness. This suggests that reproductive success, probably the most important component of population cage fitness, exhibits substantial epistatic interactions (though Kosuda, 1985, reports the absence of large interchromosomal epistatic effects in a non-competitive test of D. melanogaster male mating ability).

Similarly, the bulk of work on epistatic fitness interactions has centered on Drosophila homozygous for one or two whole chromosomes (20% to 80% of the genome). Homozygous fitness effects are large and easily measured while heterozygous fitness effects are generally subtle and difficult to detect (Lewontin, 1974). There are, nevertheless, a few reports of significant heterozygous epistatic fitness effects. Wasserman (1972), for example, reports that D. subobscura heterozygous for recombined chromosomes exhibited about 4% lower egg hatchability than flies heterozygous for non-recombined controls. Oshima (1963) and Kitagwa (1967) both report indirect evidence for heterozygous epistatic viability interactions in D. melanogaster. Charlesworth and Charlesworth (1975b) report a small (and insignificant) decrease in the viability of D. melanogaster heterozygous for one or two recombinant chromosomes compared to flies heterozygous for two non-recombined controls. Most interestingly, they also report a significant decrease (7%) in the number of offspring produced by females heterozygous for a balancer chromosome and recombined chromosomes compared to those heterozygous for the same balancer and non-recombined controls.

It appears that experiments designed to measure epistatic effects on relatively comprehensive measures of fitness in heterozygous flies would provide valuable insights. If strong epistatic fitness effects prove to be rare and limited to organisms with artificially high levels of homozygosity, they may be of little evolutionary interest. If they prove to be common and affect ordinary outbred organisms, they may be key to untangling many issues in evolutionary genetics. Weak epistatic fitness effects could also have profound consequences for evolution, but, given the difficulties reviewed above, weak effects may prove impossible to measure.

Acknowledgments

I thank L. Brooks and P.T. Ives for stimulating discussion, N. Miyashita for communicating unpublished results, and R. Seager and an anonymous reviewer for helpful comments.

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