Reprinted from COLD SPRING HARBOR SYMPOSIA
ON QUANTITATIVE BIOLOGY
Volume XX, 1955
Made in United States of America

GENETIC AND CHROMOSOMAL VARIABILITY IN DROSOPHILA

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The importance of genetic and chromosomal variability in evolution may be demonstrated by comparing the variability present in natural populations with the differences between species. This compares the potential variability with that useful in evolution of those forms where such systems can easily be studied. Many of the species of the Genus *Drosophila* possess several characteristics which make them most suitable for such analyses. Many strains from different localities may be bred in the laboratory to determine the genetic differences. The ordinary metaphase chromosomes so frequently used to determine the chromosome composition of a species can be examined. Differences in gene order and association can be made using the analyses of these differences in the *Drosophila* salivary gland chromosomes, as demonstrated by Painter (1933). A comparison of the metaphase and salivary gland configurations shows how many of the chromosome arms are euchromatin and how many are heterochromatin, as was done by Wharton (1943). When the number of heterochromatic arms present in metaphase and the number and size of the euchromatic arms is determined in the salivary gland chromosomes, the changes from the primitive configuration of five pairs of rods and a pair of dots (five long strands and the dots in the salivary gland nucleus) may be analyzed. Figure 1 shows some of the types of chromosome rearrangements that may occur. These include exchange of equal chromosome segments or symmetrical translocation, unequal exchange or asymmetrical translocation, and the limiting case of this type, called a centric fusion. Both paracentric and pericentric inversions are illustrated as well as addition or subtraction of heterochromatin. These types of heterochromatin modification cause changes in the chromosome configuration as well as size. Pericentric inversions in which

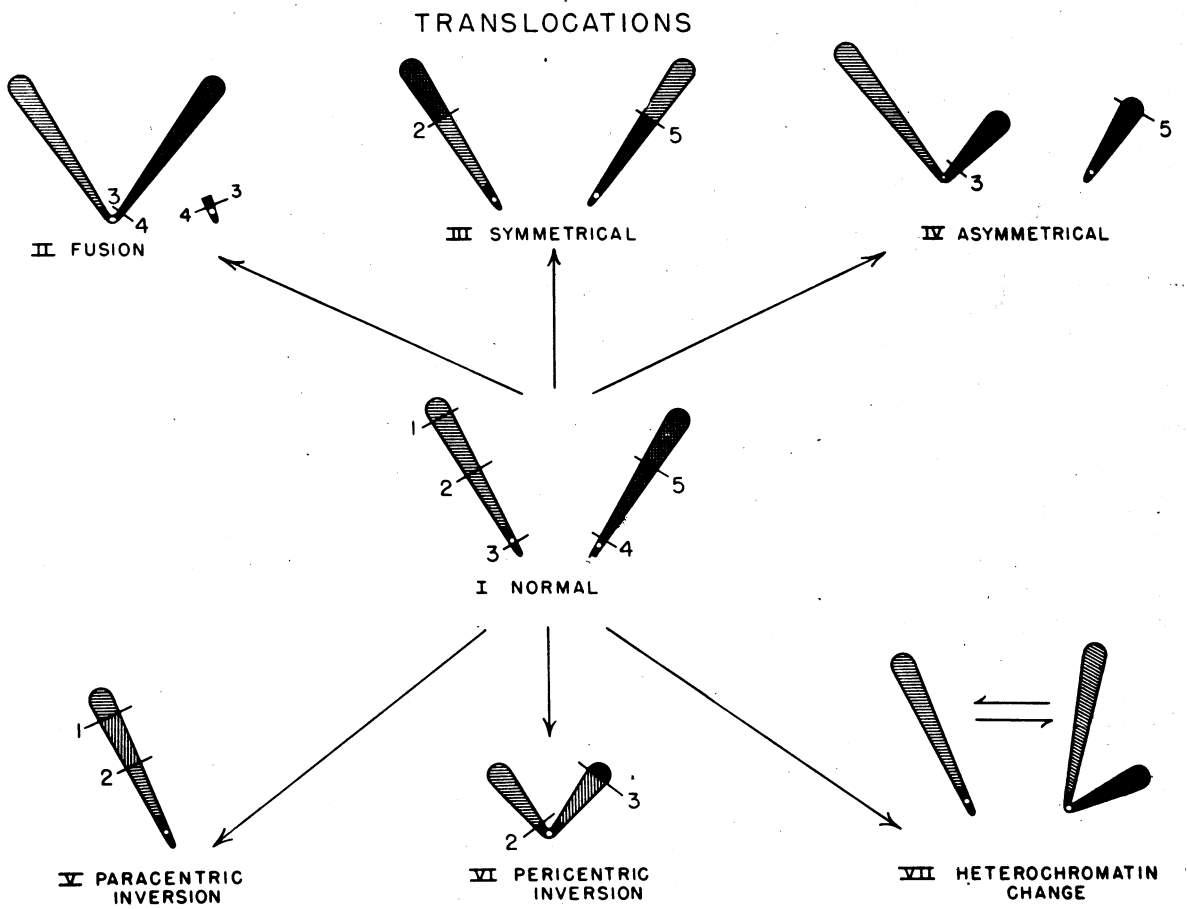

FIGURE 1. Types of chromosome reorganization.

the breakage points are sufficiently asymmetrical with respect to the centromere may be recognized by comparing the homozygotes, but paracentric inversions and symmetrical pericentrics can be detected most easily if the salivary gland chromosomes of heterozygous individuals can be examined. This restriction is true also for symmetrical translocations, but grossly asymmetrical changes may be recognized without hybridization. Hybridization allows a detailed comparison of the gene orders in the two strains or species. In favorable cases when few differences are present, similarities and differences between gene orders as reflected by changes in the banded pattern of the salivary gland chromosomes of two species can be determined accurately, except for very small rearrangements.

A comparison of the chromosome configurations including the number of arms and in some cases the banded sequences in the several chromosomes of related species may show the major cytological evolutionary changes even without hybridization. A comparison is most effective when hybrids survive to produce analyzable salivary gland chromosomes but may not be fully useful in cases of extreme cytological divergence between species, for example, the hybrids between *ambigua* and *pseudoobscura* (Buzzati-Traverso, 1950; Koske, 1953).

Chromosomal mutations are the most useful changes in the study of lineages in *Drosophila*. Gene mutations occur and recur and are mimicked by similar mutations at other loci, but each chromosomal aberration built into the cytological architecture of the related species in a species group in *Drosophila* is almost certainly the result of an unique event. As Dobzhansky (1944) points out, the probability of recurrence of the same inversion in a species is very small even though some points along a chromosome are more liable to breakage than others. This is true of the inversions within most species groups. A particular inversion represents an unique event and all descendents, in the same or related species with that gene sequence, have that one ancestor. This is also true for the relatively rare surviving pericentric inversions and for fusions, the other important class of rearrangements in *Drosophila*.

Paracentric inversions are much more nearly selectively neutral in *Drosophila* (Sturtevant and Beadle, 1936) than are pericentrics. However, Alexander (1952b) showed that the production of aneuploid gametes depended in good measure on the size and position of the pericentric inversions, so the small symmetrical types may be nearly selectively neutral. Larger or asymmetrical pericentrics are rare, for to survive they must be protected by paracentrics as demonstrated by Miller (1939). Carson (1953) studied the effect of a number of inversions present in populations of *Drosophila robusta* on the reproductive efficiency of the species. Stone (1949) demonstrated that the X-4 centric fusion present in *Drosophila americana* did not adversely affect the development of eggs laid by heterozygous females. Many investigators have shown that all other types of translocations markedly reduce the reproductive efficiency when heterozygous. Other investigators have shown that extra heterochromatin attached beyond the centromere to a rod is not usually a reproductive hazard, as, for example, the cases of XY_L and XY_S which are J-shaped chromosomes (Stern and Doan, 1936).

The importance of these laboratory studies is that they have so firmly established the chromosome mechanics in *Drosophila* that one can predict the types of chromosomal reorganizations that may be common in the genus and those that will be rare or absent. A study of between 215 and 250 species whose metaphase chromosomes are known and especially the analysis of the large fraction of this number in which the salivary gland chromosome configuration is also known proves very conclusively that our predictions are valid. For example, except for centric fusions the only translocations known to be fixed in a species are transfers of very small portions of a chromosome. The best case is that analyzed in *Drosophila ananassae* by Kaufmann (1937) and Kikkawa (1938). Much of the heterochromatin usually present in the X-chromosome, including the bobbed locus, is transferred to the dot chromosome, element F. The Y retains its heterochromatin and bobbed locus so the translocation is established as hyperploid in the male. Hsiang (1939) showed cytologically that the nucleolus organizer and much of the heterochromatin ordinarily found on the X had been transferred to the dot chromosome in *Drosophila tumiditarsus*. A few other very small translocations and tiny duplications of unknown origin have been reported. Three cases of larger heterozygous translocations have been reported from populations where they could not be recovered later. These were in *ananassae* by Dobzhansky and Dreyfus (1943), *Drosophila melanica* by Ward (1952), and in *Drosophila prosaltans*, where Dobzhansky and Pavan (1943) found a whole arm exchange between a rod and a V chromosome. All these translocation types, fusions and small transfers excepted, are at such a serious selective disadvantage due to the large numbers of aneuploid gametes produced from a heterozygote that none has been proven to have been incorporated into the cytological architecture of a new species.

The relative inefficiency of translocations such as shown in Figure 1 is best illustrated in comparison to the success of other types of chromosomal reorganization. Table 1, modified from Patterson and Stone (1952) by the addition of known new cases, shows the success of fusions, pericentric inversions and shifts in the amount or position of heterochromatin in the evolution of the analyzed species in the genus. The information is given for subgenera, and within the *Sophophora* and *Drosophila* this is further broken down into species groups. These are all minimum estimates except that the fusions in the

TABLE 1. CHROMOSOME REORGANIZATION IN THE GENUS *Drosophila*

Subgenera	Species Groups	Fusions Y-A,	X-A,	X-D,	A-A,	A-D	Pericentric X	A	D	Added Heterochromatin X	A	D
Hirtodrosophila					2		1	2				1
Pholadoris			1		1	1		1				1
Dorsilopha				1	2							
Sordophila			1					2				1
Sophophora	*saltans*		1		1	1					2	1
	willistoni		1		1	1		1				
	melanogaster			1	2		1		1			1
	obscura	1	1					3			1	1
	nannoptera		1					1			2	1
	unassigned				2							1
Drosophila	*quinaria*		1		2							1
	guttifera											
	pinicola		1		1	1						
	virilis		1		2			1				
	testacea				2			1				
	tripunctata				1	1		1			1	
	funebris											
	repleta				2					1	1	1
	annulimana					1		3		1		1
	robusta		1		1		1	1			1	1
	melanica		1		1			1				1
	polychaeta							2			1	
	carbonaria							3			1	
	cardini				2							1
	immigrans				2	1		1				1
	macroptera				1			2				
	guarani				1	1				1		1
	bizonata				2					1		
	pallidipennis									1		
	rubrifrons										1	1
	callopters					1		1			1	
	unassigned		1	1	2			1		1	1	2
	Totals	1	12	3	33	9	3	28	1	6	13	19

TABLE 2. NUMBER OF KNOWN GENE ORDERS IN THE CHROMOSOMES OF *Drosophila* SPECIES

Drosophila Species	Chromosome Element A	B	C	D	E	F	Authority
melanogaster	1	4	5	3	7	1	Dubinin *et al.*, 1937 Warters, 1944; Ives, 1947
ananassae	1	3 + 3P	2	2	3	1	Dobzhansky and Dreyfus, 1943 Freire-Maia, 1952
pseudoobscura	1	2	16	4	3	1	Dobzhanksky, 1951
persimilis	1	1	10	2	3	1	Dobzhanksky, 1951
athabasca	2	4	17	2	2	1	Novitski, 1946
algonquin	2	3	3	1	4 + 1P	1	Miller, 1939
azteca	2	1	7	3	6	1	Dobzhansky, Sokolov, 1939 Dobzhansky, 1941
virilis	1	1	1	1	1	1	Chino, 1936; Hughes, 1939
americana	3	4	3	2	3	1	Hsu, 1952
novamexicana	1	1	1	1	1	1	Hsu, 1952
littoralis	1	2	1	2	1	1	Hsu, 1952
lacicola	1	2	5	1	5	1	Hsu, 1952
boralis	1	1	2	3	2	1	Hsu, 1952
flavomontana	1	2	1	1	2	1	Hsu, 1952
montana	4	15	2	3	4	1	Hsu, 1952; Moorhead, 1954
Total 15	23	46 + 3P	76	31	47 + 1P	(15)	223 + 4P Average = 3 per arm

saltans and willistoni groups probably have a common origin. As given in the table, there are at least 55 fusions, 32 pericentric inversions, and 38 shifts in heterochromatin in the analyzed cases. This does not include changes in the Y-chromosome.

The number of paracentric inversions cannot be estimated in this manner but some idea can be obtained from the special analyzed cases. Tables 2 and 3 are an analysis of the cytological variation in terms of inversions. The figures indicate how many different gene arrangements (including the standard) are known in each chromosome. This is not a complete list for it omits a number of cytologically homogeneous species and a few others. Such a list

TABLE 3. NUMBER OF KNOWN GENE ORDERS IN THE CHROMOSOMES OF *Drosophila* SPECIES

Drosophila Species	Chromosome Number						Authority
	X	2	3	4	5	6	
repleta (and 15 others)	1	1	1	1	1	1	Wharton, 1942; Wasserman, 1954
canapalpa	1	2	1	1	1	1	Wharton, 1942; Ward and Stone, 1952
melanopalpa	1	2	1	1	1	1	Wharton, 1942 Ward and Stone, 1952
hydei	1	2	1	1	1	1	Warters, 1944
nigrohydei	1	3	1	1	1	1	Wasserman, 1954
buzzatii	1	2	1	1	1	1	Wasserman, 1954
paranaensis	1	1	3	1	1	1	Wasserman, 1954
mercatorum	1	1	4	1	1	1	Wasserman, 1954
subobscura	3	2	5	6	12	1	Stumm-Zollinger, 1953
obscuroides	2	2	2	1	1	1	Mainx, Koske and Smital, 1953
ambigua	3	3	1		2	1	Mainx, Koske, Smital, 1953
bifasciata	2	2	1		1	1	Mainx, Koske, Smital, 1953
tristis	1	1	5		3	1	Mainx, Koske, Smital, 1953
funebris	1	4	2	2	1	1	Dubinin, Tiniakov, 1947
macrospina	1	7	1	2	3	1	Warters, 1944 Weinberg, 1954
guaramunu	1	2	3	26	4	1	Brncic, 1953; Salzano, 1954
griseolineata	1	4	3	1	1	1	da Cunha *et al.*, 1953
melanica	6(LR)	17	1	3	1		Ward, 1952
	XL	XR	2L	2R	3		
robusta	4	4	4 + 1P	2	1 + 1P(L) 2(R)		Carson, Stalker, 1947
willistoni	9	6	9	7	15		da Cunha, Dobzhansky, 1954 Dobzhansky *et al.*, 1950
tropicalis	1	1	4	1	2		Dobzhansky, 1955
paulistorum	6	3	5	5	15		Dobzhansky *et al.*, 1950
equinoxialis	1	1	1	1	2		Dobzhansky *et al.*, 1950
nebulosa	2	1	1	1	12		Pavan, 1946 da Cunha *et al.*, 1953
bocainensis	2	3	4	2	7+		Carson, 1954
parabocainensis	1	1	2+	2+	1		Carson, 1954
bocainoides	1	2	1	2	1		Carson, 1954
Total 27	56	80	68 + 1P	72	93 + 1P		369 + 2P Average = 2.73 per arm

necessarily gives the minimum number—only those inversions so far demonstrated. Table 2 gives the species where chromosome homologies are known (Muller, 1940; Sturtevant and Novitski, 1941; Spencer, 1949; Patterson and Stone, 1952). This allows a direct comparison between different species. Table 3 gives the chromosomes by the numbers usually employed. Comparable numbers are not always equivalent elements, although they usually are within species groups. Only a few key references are given.

The analysis of the 15 species where the elements may be compared shows no inversions heterozygous within the dot. Inversions do occur in this element, however, for Horton (1939) and Slizynski (1941) showed that the fourth chromosome, element F, of *Drosophila simulans* differed from that of *Drosophila melanogaster* by an inversion. All five major elements vary: A = 23, B = 46 + 3 pericentrics, C = 76, D = 31, and E = 47 + 1 pericentric. Ignoring the dot, this is 223 inversions in 75 elements in the 15 species or an average of three per element. The actual distribution is by no means uniform because of the concentration of inversions in element C in the American members of the obscura group.

There is no way to make a satisfactory comparison of equivalent chromosomes of the species listed in Table 3 except within the species group. In the 27 species there are 369 paracentric and 2 pericentric inversions, an average of 2.7 for each of the five large elements. At least 18 species have no known inversions, but the majority of species have a few and some species have a larger number. Of the species listed in the two tables which have at least 20 inversions, *pseudoobscura, guaramunu, athabasca, montana,* and *melanica* have a disproportionate number in one chromosome and few in the others, while *subobscura, willistoni,* and *paulistorum* have a number in each chromosome.

The role and comparative usefulness of pericentric and paracentric inversions in the cytological

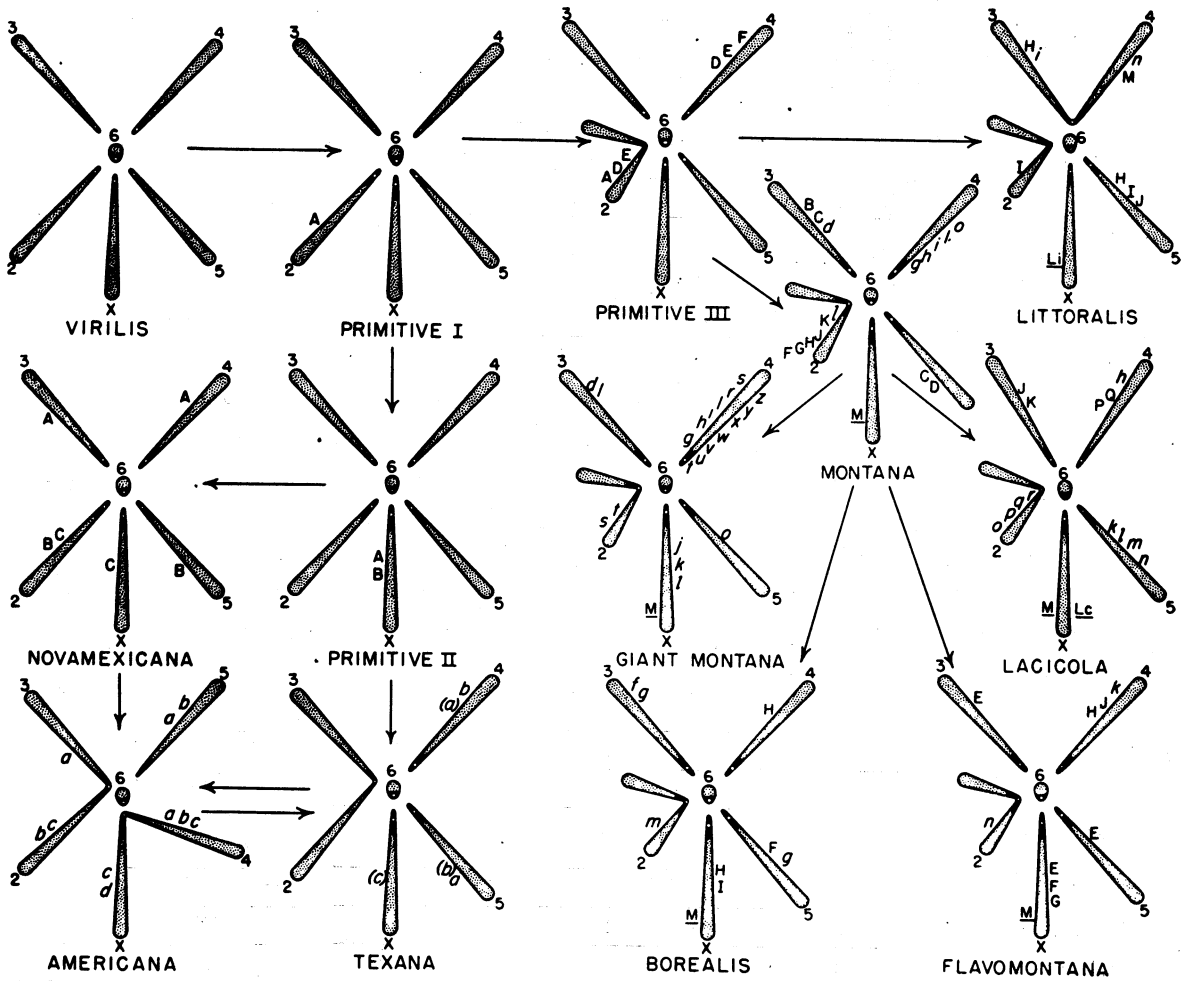

FIGURE 2. Chromosome evolution in the virilis group after Hsu (1952). Capital letters indicate inversion fixed in species; lower case italicized letters indicate inversions present sometimes. Arrows indicate sequence used. Each species has all inversions indicated homozygous earlier in sequence or has exceptions indicated.

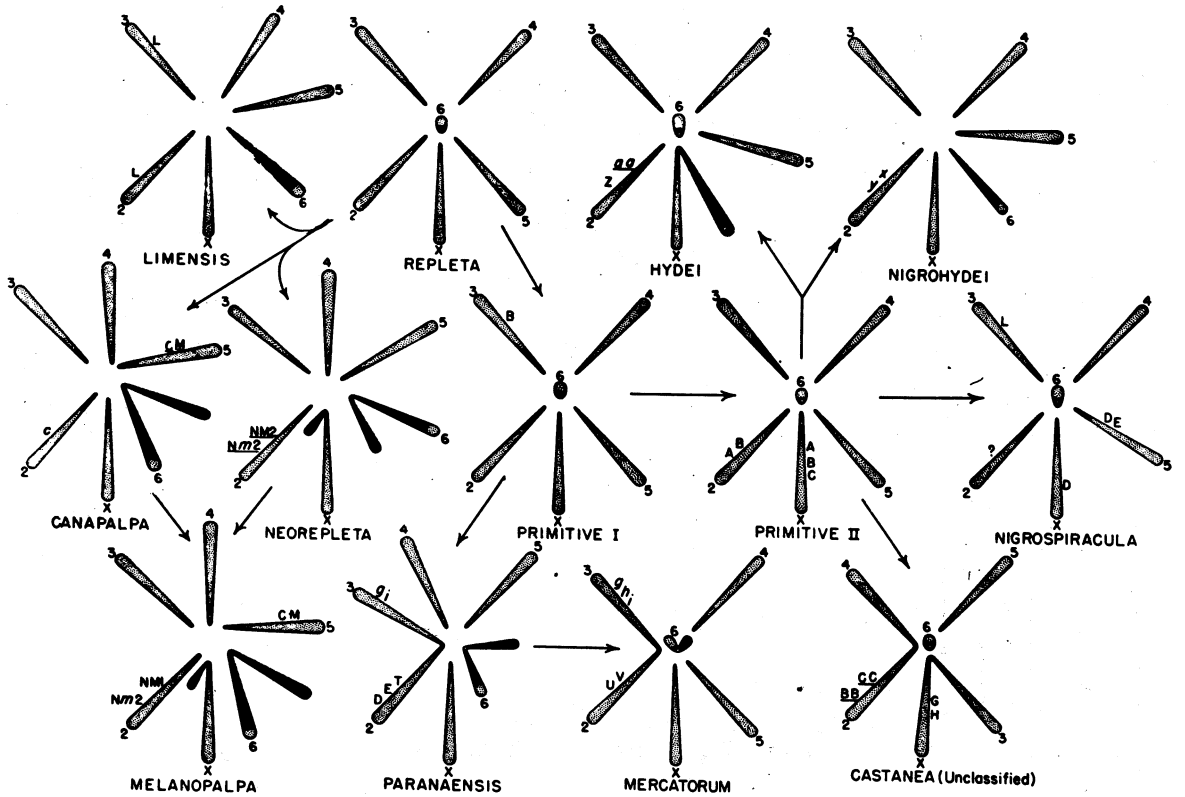

FIGURE 3. Evolution in the repleta group after Wasserman (1954). (See Fig. 2 for explanation.)

evolution in the genus is best seen in two analyses of species groups, the virilis group by Hsu (1952), Figure 2, and the large repleta group by Wasserman (1954), Figures 3 and 4. In each of these groups we have used the most primitive living species, *virilis* and *repleta* respectively, as the center of the group. They differ from the cytologically primitive ancestor by one inversion if at all, that is, the cytological configuration given as Primitive I might be the primitive ancestor in each group. In these figures the presence of a letter indicates the origin of a new inversion. Capitals indicate that the new inversion is always present and small letters that it is only sometimes present. The arrows indicate that the subsequent species in the sequence have all the indicated inversions homozygous. In only a few cases was it necessary to repeat a letter in a derived species to show relationships best.

In the ten forms in the virilis group there are eight species, including two which are divided into subspecies. There are known in addition to the *virilis* sequence: (a) 12 inversions (8 homozygous, 4 heterozygous) in the X (element A); (b) 20 inversions (11 homozygous, 9 heterozygous) in chromosome 2 (element E); (c) 12 inversions (7 homozygous, 5 heterozygous) in chromosome 3 (element D); (d) 26 inversions (9 homozygous, 17 heterozygous) in chromosome 4 (element B); and (e) 15 inversions (8 homozygous, 7 heterozygous) in chromosome 5 (element C). This is a total of 85 inversions and there are several others in each of the X-chromosomes of *montana*, *lacicola*, and *littoralis* so that these X's could not be analyzed for lack of forms with intermediate sets of inversions. There are 42 inversions which occur only as heterozygotes while 43 have been used in the basic chromosome architecture of one or more of the species. Among these latter, 4 *h* is also heterozygous in *montana* and *lacicola*, and X *c*, 2 *bc*, 3 *a*, 4 *a*, and 5 *b* are heterozygous in *americana* but homozygous in *novamexicana*. This is a ratio of 43 inversion sequences fixed in the evolution of the group to 49 inversions that show as heterozygotes in some of the species.

A similar analysis can be made in the repleta group. In addition to the *repleta* gene sequences there are: (a) 8 inversions in the X-chromosome, all homozygous; (b) 33 inversions in the 2 chromosome, 27 homozygous and 6 heterozygous; (c) 10 inversions in the 3 chromosome, 7 homozygous and 3 heterozygous; (d) 0 inversions in the 4 chromosome; and (e) 6 inversions in the 5 chromosome, all homozygous. This makes a total of 9 inversions that occur heterozygous in some species to 48 used in basic alterations in chromosome sequences. In the virilis group there are about 9/10 as many basic species rearrangements as there are heterozygous inversions. This is an underestimate on basic se-

quences, for at least 15 added inversions are present in the X (X_M, X_{Lc}, X_{Li}). If we were to add this conservative estimate, there are at least 1.2 times as many inversions fixed as heterozygous. In the cytologically conservative repleta group, there are 5.4 times as many species arrangements as heterozygous inversions. These ratios may be used to calculate the number of paracentric inversions used in rebuilding the chromosomes in the genus. All told, there are 592 heterozygous inversions known in populations of the 42 species listed in Tables 2 and 3 plus 15 homozygous members of the repleta group, shown in Figures 3 and 4. Using the ratios of inversions fixed in species to those heterozygous, one estimates that somewhere between 533 (based on the virilis group) and 3200 (based on the repleta group) inversions were utilized in the cytological evolution of the 57 species. Using this estimate there will have been between 6,100 and 36,500 paracentric inversions used in the evolution of the 650 species which M. R. Wheeler estimates are now listed for the genus. There are additional undescribed species, and for this and other reasons even the higher figure is probably an underestimate.

The less frequent types of chromosome reorganizations in these two species groups are few. Only one pericentric inversion and three fusions have occurred in the virilis group. Including *Drosophila castanea*, although it may belong in a separate group, there are in the repleta group four fusions and a minimum of three additions of heterochromatin to make rod-shaped chromosomes into J's and V's, or increase the size of the dot. These numbers are very small but agree as well as could be expected with the estimated frequencies of these several types of rearrangements (Table 1). The numbers in this table represent about a third of these types of chromosomal reorganization in the genus.

Gene mutations are those inter- and intramolecular changes and rearrangements in the chromosome which are too small to see with the light microscope. Although our knowledge of the chemical structure of the chromosomes is increasing very rapidly, we have not begun to determine the chemical composition or structure of a gene. We can only measure changes in gene organization and association by their effect on the cell, tissue, or organism.

Many studies have been made on lethal mutations. Dominant lethals include both chromosome abnormalities and haplo-insufficient genes. Recessive mutation rate has been measured very extensively. This gives us some measure of the frequency of mutation to alleles which do not carry out some irreplacable action or which carry out the wrong ac-

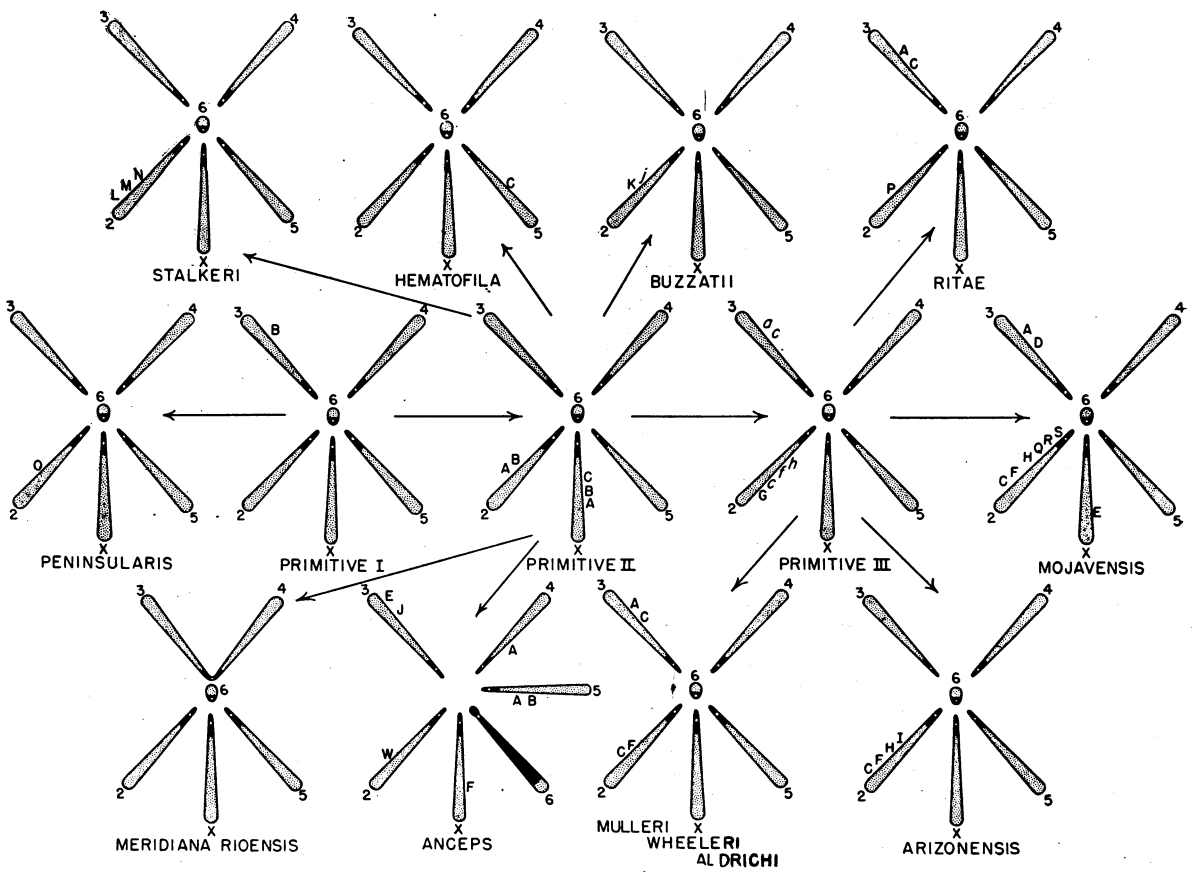

FIGURE 4. Evolution in the repleta group (continuation of Fig. 3).

tion in that genetic system. It does not measure the rate of mutation of alleles produced with a low frequency in *Drosophila*. We must regard lethal mutations as unimportant in the evolution of one genotype even though a few of them may be used in the evolution of another genotype with a different genic balance.

A most interesting and useful class of mutations to consider as material for evolution are the visible mutations. Another important class are the mutants causing heterosis. The visible mutations have been extensively collected and analyzed in a few species: *Drosophila melanogaster* especially by Bridges (Bridges and Brehme, 1944) and Dubinin and collaborators (1934, 1936); *Drosophila virilis* by Metz, Moses and Mason (1923) and Chino (1936, 1937, 1941); *Drosophila ananassae* by Moriwaki (1937, 1938) and Kikkawa (1938); *Drosophila pseudoobscura* by Crew and Lamy (1935), Donald (1936), and Sturtevant and Tan (1937); *Drosophila buschii* by Krivshenko (1941, 1950, 1955); *Drosophila hydei* by Spencer (1949). Not only were very many mutations recovered and studied but also gene homologies were established between these species and several others which have not been so thoroughly investigated. Muller (1940) established the concept of chromosome elements based on the chromosomes of *Drosophila melanogaster*. Element A is equivalent to the X, B to 2L, C to 2R, D to 3L, E to 3R, and F to the 4 or dot chromosome. These elements are the chromosome equivalents determined by Sturtevant and Novitski (1941), who established most of the cases used in Table 2, and Spencer (1949) who discussed *hydei*. Instead of reviewing the older work, the unpublished data of Professor W. P. Spencer on visible mutations and homologies in *Drosophila mulleri* will be presented.

Professor Spencer collected *Drosophila* from November 5, through December 15, 1954 by his house in Austin, Texas. His backyard is adjacent to a park with a stream. In the collecting area, 100 × 40 feet along the stream (an area one two-billionth the size of Texas according to his calculations), he caught 15,409 *Drosophila* representing 23 species. The most abundant species was *Drosophila mulleri*, of which 3518 males and 3290 females were captured. He obtained offspring from 736 F_1 cultures of pairs of captured flies. He inbred, using mass matings, as pair matings are difficult with *mulleri*, and obtained 263 mutants. A few were duplicates or did not breed true. His earlier experiments with *Drosophila immigrans* and *hydei* indicate that ⅓ to ½ as many mutants are found in mass cultures as are found from the progeny of three pair matings. Spencer estimates that there were between 900 and 1400 visible mutants in the 1472 wild flies tested, or from 0.6 to 1.0 mutant per fly. This frequency of mutant per fly is comparable to the results of his earlier studies with *Drosophila hydei* and *Drosophila immigrans*, somewhat higher than his figures for *Drosophila robusta*, but lower than those for *Drosophila melanogaster* and *Drosophila simulans*. Alexander (1949, 1952a) obtained somewhat higher figures (between one and two mutants per fly) for *Drosophila limpiensis*, *Drosophila americana americana*, *Drosophila americana texana*, and *Drosophila hydei* but she included some widespread mutants while Spencer did not count bobbed which is widespread in *hydei*. Alexander (in Stone, Alexander, and Clayton, 1954) found fewer mutants (about 0.4 per fly) in *Drosophila novamexicana*, which lives in small linear populations. Several flies in the population of *mulleri* had the same mutant indicating a considerable kinship. This is best illustrated by the bright scarlet-like eye colors. These four different loci were represented as follows:

(a) 10 recoveries of scarlet 189—Chromosome V, homologous to scarlet in element D (the number 189, etc. refers to stock 189 and the chromosome numbers refer to homologous numbers used in *hydei*).
(b) 5 recoveries of scarlet 205—Chromosome III, homologous to cinnabar in element C.
(c) 5 recoveries of scarlet 90—Chromosome II, homologous to cardinal in element E.
(d) 1 recovery of scarlet 183, which is phenotypically different from the others, — Chromosome III, element C.

Table 4 shows a list of mutants which have already been proven to be linked on the several chromosomes. Those in italics are homologous to mutants on those elements in *melanogaster* or *hydei*.

Approximately 40 mutants in stock have not yet been located as to chromosome. The small amount of autosomal linkage data so far collected indicates long autosomal maps as in other species of the subgenus *Drosophila* for which linkage data are available.

An interesting example of the validity of homologies and cytological comparisons is illustrated by Spencer's X-chromosome maps, Figure 5. Wasserman (1954) decided that the X-chromosome of *mulleri* and *hydei* were physically alike. Spencer's maps show that crossing over is similar in the two species. In fact, the homologous genes, carnation, vermilion, and light recombine about the same in the two species and other probable homologies are similar in their linkage.

Several conclusions may be drawn from these data. The homologies show that *Drosophila* species in different subgenera still give equivalent mutations. From this we can infer that the normal alleles of the homologous mutants have at least related if not identical effects which are important to members of the genus. There is a tremendous number of mutants present in *Drosophila*. In such a population as Spencer sampled of *mulleri*, a conservative estimate would indicate the presence of a different mutant in every other fly. This does not

mean that in the tremendous populations of most species that every other fly has a different mutant, even restricting them to visible mutants which are only one class of phenotypic result. It does mean that these populations, even in restricted localities, possess a tremendous store of concealed genetic variability which can be used by the population if any combination becomes advantageous. Even with a conservative mutation rate, the incidence of mutation in members of the genus *Drosophila* is quite high.

The adaptive advantage of these visible mutants has been questioned. Many of them do not seem useful under most circumstances. This is to be expected on the theory of evolution through mutation and natural selection. The real question is whether part of them may be useful. This can be answered only by comparing the differences in characters between related species with the differences produced by mutations. We have the following good examples from Spencer's unpublished work on *mulleri*.

The repleta group as contrasted to most other *Drosophila* is characterized by spotting on the thorax. This is a pattern effect with the pigment concentrated around the bristles and hairs and missing many places in between. Spencer has found a mutant in *mulleri*, homologous to a mutant in *hydei*, which makes the pattern of pigment uniform. This mutant, Extension, is a semidominant located on the dot chromosome, element F. The heterozygote makes the pattern of *hydei* or *mulleri* resemble that of *Drosophila californica* and *Drosophila fuliginea*. These species would be the type expected from an intermediate allele or modifiers. When Extension

TABLE 4. LINKAGE OF MUTANTS IN *Drosophila mulleri*

X Chromosome (Element A)

bobbed
forked
garnet-like
light—body color
lozenge
vermilion
dusky (mosaic)
singed (mosaic)
miniature (lost)

Chromosome II (Element E)

61 brown-like
262 *curled*
42 peach-like
295 peach-like (possible allele of 42)
468 *polychaete* (many extra bristles on thorax)
144 purple-like
90 *cardinal*
160 two-joint (middle three tarsal joints missing)

Chromosome III (Element C)

484 *brown* (white or almost white double recessive with scarlet)
205 *cinnabar*
42 cup wing (wings much reduced in size and often cup shaped)
298 *lanceolate* (long narrow wings tapering to a point)
109 peach-like
127 purple-like
644 *rolled* (thin textured wings rolled under at the tip)
183 scarlet-like (but easily distinguishable from scarlet—not allele of cinnabar)
470 serrated (wing margins scalloped—very slight dominant effect but no overlap with the recessive)
454 thin (wings thin textured)

Chromosome IV (Element B)

256 *elbow* (wings broad and convex dorsally—crossveins broken or missing)
170 bent down (wings bent down at tips—normal overlaps)
303 dark brown-like
341 warped-like (allele of 170 bent down, but no normal overlaps)

Chromosome V (Element D)

31 brown-like
135 dumpy-like (but lacks whorls on thorax)
95 fringe (bristles on margin of wing irregular)
120 *inturned* (bristles stand out on wing margin; abdominal hairs irregular; dorso-centrals turned toward midline)
682 *javelin*
272 peach-like
120 reinforced (extra vein along posterior margin of wing)
189 *scarlet*
433 *sepia*
269 sparse (hairs and bristles on margin of wing sparse)

(Chromosome VI (Element F)

456 *eyeless*
Extension (homologue in *hydei*—heterozygote easily separable from wild-type and homozygote)

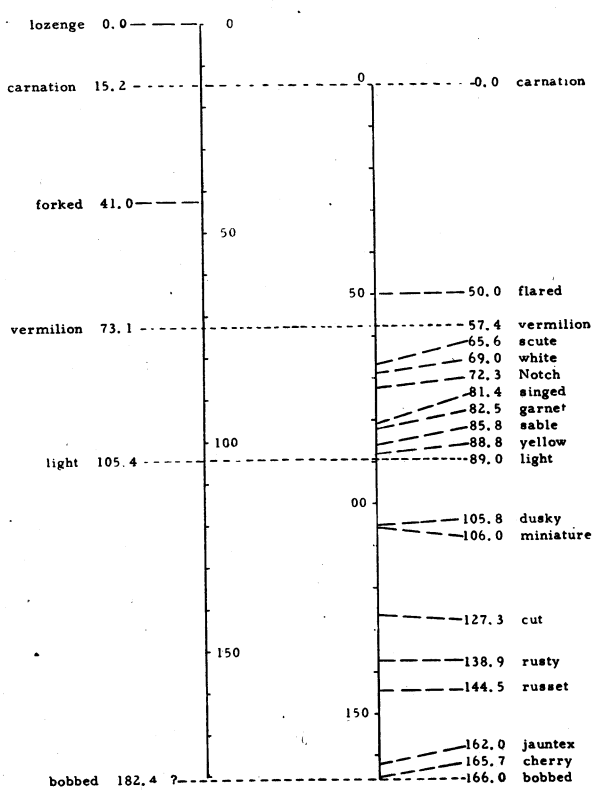

FIGURE 5. X-chromosome maps of *Drosophila mulleri* (left) and *Drosophila hydei* (right) by Spencer.

is homozygous, the affected members of the repleta group resemble in color pattern more nearly members of the virilis or robusta groups with their dark dull background color. The mutant, light, in *mulleri* causes a loss and shift in pigment so the color and pattern are more like *Drosophila mojavensis* and *Drosophila ritae* and others. The mutant polychaete adds bristles to the thorax somewhat like those in *Drosophila testacea* and *Drosophila polychaeta*. Another mutant in *mulleri* called depigmented causes the pattern to resemble that in *Drosophila hexastigma*. Most of these mutants cause *mulleri* or *hydei* to resemble more closely other members of the group, which is to be expected. The semi-dominant mutant Extension suggests that a fairly simple mutant change in the ancestor of the group may have restricted the pigment and produced the characteristic spotted pattern of this species group. In this connection it is of interest that similar spotted pattern occurs in at least seven other families of flies, according to M. R. Wheeler.

The gene differences between related strains which control isolation between species represent a class of mutations which have selective and adaptive advantage. Genetic differences between strains, sometimes even a one gene difference, may be very important in effecting isolation between species. Crow (1942) demonstrated a sex-linked dominant cross-lethal gene in *Drosophila aldrichi* which caused *mulleri-aldrichi* hybrid females to die. This gene was present in only some of the individuals in the *aldrichi* population. Patterson and Griffen (1944) found a dominant mutant located in the left end of the X-chromosome of *Drosophila americana texana* which caused *montana-texana* hybrid female zygotes to die when the cross involved *montana* egg cytoplasm. This factor was not present in the subspecies *americana*. Some recent work of Patterson (1954) shows these major differences in isolating factors within a species. These are illustrated by crosses between *Drosophila novamexicana* (N, stock 1714.4 from San Antonio, New Mexico) or *Drosophila littoralis* (Li, stock 2000.1 from Merlingen, Switzerland) and four strains of *Drosophila virilis*. These are Va (stock 1999 from Chaco, Argentina), Vb (stock 2207.1 from Agudo, Brazil), Vc (stock 2215 from Santiago, Chile), and Vm (stock 1801.1 from Texmelucan, Mexico). The *virilis* strains show no isolation or other such genetic differences in crosses to each other.

Table 5 shows marked genetic differences between these *virilis* strains in crosses to *novamexicana* and *littoralis* resulting in differences in sexual isolation, cross-fecundity, and F_1 and F_2 fertility. In some cases cross-insemination is prevented, in others the presence of alien sperm does not insure the production of hybrids. The great importance of these isolating factors in the reproductive economy of the genus has been discussed at length by Dobzhansky (1951) and Patterson and Stone (1952). The point to be stressed in connection with genetic variability in the genus is that four stocks chosen at random from different localities showed such differences.

One important demonstration of genetic variability is the very frequent occurrence of heterosis when members of two populations are crossed (Dobzhansky, 1951, 1952; Brncic, 1954; Cordeiro, 1952; Cordeiro and Dobzhansky, 1954; Vetukhiv, 1953, 1954; Stone, Alexander and Clayton, 1954). In addition to this general type of heterosis there is a special type which depends on the presence of two or more gene arrangements in the same population (Dobzhansky, 1951, 1952, 1955; Dobzhansky and Pavlovsky, 1953; Levene, Pavlovsky, and Dobzhansky, 1954; da Cunha and Dobzhansky, 1954; Epling, Mitchell, and Mattoni, 1953; and Townsend, 1952). Dobzhansky and Levene (1948) showed that inversion heterozygotes were heterotic in natural populations of *Drosophila pseudoobscura*. This observation has been extended to include many other species (see references above) but is not uni-

TABLE 5. CROSSES BETWEEN FOUR *virilis* STRAINS AND *novamexicana* OR *littoralis*

Crosses ♀ ♂	Number tested	Offspring ♀♀	Offspring ♂♂	$F_1 \times F_1$ ♀♀	$F_1 \times F_1$ ♂♂	Fertility of F_1 hybrids ♀♀	Fertility of F_1 hybrids ♂♂	$F_2 \times F_2$ % fertile	
Va × N	100	395	408	0	0	fert.	st.		
Vb × N	100	195	181	135	114	fert.	fert.	32% (30.0)	
Vc × N	100	214	203	1	1	fert.	fert.		
Vm × N	100	212	242	0	0	fert.	st.		
N × Va	100	19	17	98	76	fert.	fert.	17% (7.1)	
N × Vb	100	42	42	97	85	fert.	fert.	6% (11.3)	
N × Vc	100	59	54	175	118	fert.	fert.	33% (27.1)	
N × Vm	100	42	48	71	51	fert.	fert.	23% (9.5)	
Va × Li	100	18	21	0	0	fert.	st.	Dissected	Inseminated
Vb × Li	100	0	0					58	3
Vc × Li	100	26	20	0	0	fert.	st.		
Vm × Li	100	33	37	0	0	fert.	st.		
Li × Va	100	0	0					40	17
Li × Vb	100	3	2	0	0	st.	st.		
Li × Vc	100	0	0					56	3
Li × Vm	100	0	0					59	2

versal. Salzano (1955) showed that several inversions were present in populations of *Drosophila guaramunu* in approximately a Hardy-Weinberg equilibrium. In fact, the two gene sequences E and e were present more often than expected homozygous (EE and ee) and too seldom heterozygous (Ee). Salzano concluded that the frequency of the heterozygote was reduced because of selection against it, that is, both homozygotes have a higher selective value than the heterozygote. Furthermore, da Cunha (1951) and Dobzhansky and Spassky (1954) showed that the adaptive values of certain genotypes varied with the environmental conditions.

Dobzhansky (1951) and Patterson and Stone (1952) reviewed the evidence on genetic variability of natural populations. Since then Dobzhansky and Spassky (1954) published a study of *Drosophila prosaltans* and Pavan and Knapp (1954) reported their tests with *Drosophila willistoni*. The incidence of lethal and semi-lethal mutations in the second chromosome of this latter species was 41.5 ± 1.0 per cent. Although the genetic diversity of the species with more restricted distributions and populations is smaller, for example, *pseudoobscura* (Wright, Dobzhansky, and Hovanitz, 1942), *prosaltans* (Dobzhansky and Spassky, 1954), and *novamexicana* (Stone, Alexander, and Clayton, 1954), all of these species and all others studied possess a spectrum of mutant alleles ranging from lethals to heterotic genes in their natural populations. This seems to be characteristic of this genus and related genera of the Drosophilidae for Stalker (1954) showed that *Scaptomyza graminum* had a greater frequency of hidden recessive mutations than many *Drosophila* species. The genetic variability of *Drosophila* is equivalent or greater than that shown by comparing the races of maize in Mexico (Wellhausen *et al.*, 1952). Unlike maize, the genetic variability usually depends on heterozygosity of mutants in phenotypically similar strains of *Drosophila*. These populations are usually heterozygous for the recessive mutations and lethals which are at a selective disadvantage when homozygous. Despite the great numbers of mutations present, most members of the population are normal in phenotype. Many of the genes which cause heterosis are present because of their advantage in the heterozygote, but it is impossible to tell how many of them are beneficial mutations fixed or on their way to fixation.

Da Cunha and Dobzhansky (1954) presented very considerable evidence that the extent of chromosome polymorphism in *willistoni* was directly correlated with extent of environmental polymorphism. They propose that the increase in amount of chromosome polymorphism in regions with many ecological niches is a multiple adaptive system to exploit the more variable environment. Levene (1953) has supported this postulate on mathematical grounds and Mather (1955) may be considered to support them with his comments on the occurrence of polymorphism due to disruptive selection in a complex environment. The problem may be stated in another way. The desert species, including many of the repleta group, seldom have an appreciable chromosome polymorphism. We can deduce that in harsh difficult environments with few adaptive niches species cannot afford the luxury of chromosome polymorphism. It would seem that the advantage of free recombination is too useful to these smaller populations and not even the almost universal occurrence of heterosis between the restrictive inversion genotypes can bypass the selective advantage of free trial of all possible gene combinations. This does not mean that evolution cannot go on. The repleta group, having achieved the ancestral genetic system which made desert adaptation possible, has evolved into the largest species group in *Drosophila* with over fifty species, sometimes without any cytological differences (Figs. 2 and 3). The frequent occurrence of mutations causing sexual isolation, as shown in *repleta* by Wharton (1942), disruptive selection and small population size must all have contributed to the rapid formation of species in this group. The desert conditions which lead to a situation resembling the island migrants in peripheral populations has been discussed by Mayr (1954).

In other groups some of the species have achieved considerable chromosome polymorphism without being one of the more successful species in a region. Moorhead (1954) showed that the form (or subspecies) "giant" *montana* had 21 inversions heterozygous, but it is not one of the large populations in the Pacific Northwest. Some of the dominant *Drosophila* species have achieved this cytological versatility, for example, *pseudoobscura* in the western United States and *willistoni, paulistorum*, and *guaramunu* especially in Brazil. Nevertheless, da Cunha and Dobzhansky (1954) showed that *willistoni* was cytologically conservative in the desert area and even in some environmentally very rich regions. In these forms chromosomal polymorphism is associated with tremendous populations in a large favorable area. An interesting point in this connection is that no one of the eight species which have been able to establish themselves in all eight of the faunal realms of the world is cytologically very versatile. None depends on cytological polymorphism. Indeed, two members of the repleta group, *repleta* and *hydei*, are included in these eight and *virilis* occurs in four of the six realms. These species have achieved their adaptive versatility without cytological polymorphism.

Chromosomal abnormalities and mutations, including both lethals and visibles, seldom have a selective advantage. We must not forget that there are visible mutations which simulate the phenotype of related species. These mutant alleles or their phenotypic equivalents have been used in a different genic balance system in evolution in the genus.

There is one group of mutations which differs from population to population. These are the genes which produce heterosis in crosses between strains from different localities or produce inversion heterosis. Of all the categories referred to above, the genes which produce heterosis represent the only large class which shows selective advantage. Others may have selective advantage in different genetic combinations, and alternate alleles have been used to produce diverse phenotypes in related species.

Haldane (1954) stressed the importance of heterosis in the fundamental processes of evolution. Not only are there heterozygous genotypes within any population, but also crosses between populations usually result in heterosis. In many cases this heterosis must result from heterozygosity of genes which are homozygous in the parent strains. This indicates a simple beneficial effect of migration in the evolutionary process. The problem of gene action and interaction leading to heterosis has been developed especially by Emerson (1950, 1952), and discussed further by Rendel (1953) and by Stone, Alexander, and Clayton (1954). Wagner and Mitchell (1955), who developed this field of biochemical genetics in a series of publications, summarize much of the information on gene interactions in biochemical synthesis. The importance of gene interaction in heterosis has been developed also by Robertson and Reeve (1955, see bibliography also). The importance of the differences between the alleles of genes along linked reaction chains in biochemical synthesis leading to the phenotypic characteristics of the organisms is abundantly documented in the work with *Neurospora* and *Drosophila* and also in mammals in a series of studies by Wright and his students (Wright, 1949; Wright and Braddock, 1949; Wolff, 1955; see these bibliographies also). The "hybrid substance" and other interaction effects found among the genetically determined antigens in species crosses in the Columbidae by Irwin (1953, and references) and his collaborators are examples of the importance of gene interactions in the fundamental chemical architecture of the cell. Heterosis is an evolutionary "foresight" mechanism which conserves the variability made available by mutation and increases the flexibility of the genetic system for diverse adaptations.

In this paper the role of chromosome rearrangements has been stressed because of the small number and unique nature of the rearrangements in a species. The number estimated for the evolution of the genus is certainly an underestimate. The number of different visible mutations and those causing less easily detected physiological changes such as lethals and sterility factors is perhaps greater within one successful species such as *willistoni* than all the paracentric inversions used in remodeling the cytological architecture of the genus.

The high frequency of heterosis on crossing different strains shows that there are continually being provided mutants which are of selective advantage under at least some circumstances. The genetic differences have culminated in fundamental genic balance differences between species. Patterson and Stone (1952) reviewed the extensive evidence from F_1 and recombination hybrids on the extent of these differences in genomes. Although cytological modifications of the type considered here are common and probably often important in the evolution of the genus, the fundamental changes have been the organization of different balanced gene systems.

Acknowledgments

I wish to thank Professor Warren Spencer for the use of his unpublished data on *Drosophila mulleri* and Professor J. T. Patterson for his data. Also, I wish to thank Dr. Marshall R. Wheeler and Professor Spencer for reading and making suggestions about the manuscript.

The investigations of the genetics group of the University of Texas which is included here was supported by the Rockefeller Foundation.

I wish to thank The Macmillan Company for permission to use Table I which is a modification of Table 28, Patterson and Stone, Evolution in the Genus Drosophila.

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DISCUSSION

A. ROBERTSON: Segregation at a single locus, at which the heterozygote is superior in fitness, obviously means that the average fitness of all individuals is below that of the heterozygote. If there are many such independent loci, the multiple heterozygote may be much fitter than the population mean. As there is an upper limit to some components of fitness, such as the hatchability of eggs, the spare reproductive potential of the species (the difference between the fitness of the best individual and that needed to maintain the population) may limit the number of overdominant loci which we will find in a population.

This has perhaps some bearing on the origin of balanced inversions. If there is complete breakage between the overdominant loci, it can be shown that the fitness of the population will be higher than if

they are segregating independently. The inversion system would thus be a mechanism for receiving the maximum possible proportion of individuals heterozygous for all loci simultaneously. Overdominance at individual loci could then lead to the establishment of pseudo-overdominance between inversions.

FREIRE-MAIA: The following table summarizes the data we have obtained regarding chromosome polymorphism in Brazilian domestic species:

Drosophila Species	Number of individuals examined (N)	Number of different inversions	Number of heterozygous inversions (n)	Mean number of heterozygous inversions per individual (n/N)[1]
ananassae	1373	24[2]	1945	1.42
pararepleta	26	7	29	1.12
melanogaster	521	13	335	0.64
immigrans	110	2	31	0.28[3]
kikkawai	263	1	33	0.13[4]
hydei	155	2	9	0.06
simulans	513	0	0	0
repleta	55	0	0	0

Observations: 1. These frequencies do not seem to present a positive correlation with the ecological versatility of the respective species, as was shown mainly by Dobzhansky, da Cunha and Burla for several wild species.

2. These include five pericentric inversions (4 in chromosome III and one in chromosome II). As four of these have been found only once each, and one has been found four times in two different localities, their total frequency equals 0.58%. It is interesting to observe that this number of pericentric inversions is higher than that detected in natural populations of all the other *Drosophila* species put together.

We have found also in *ananassae* one translocation (IIIR-IIR), one deletion (IIL), two transpositions (II and III) and a great many "extra bands" in all the chromosome tips. Some of these "terminal" extra bands show a very clear heterochromatin nature. It deserves mention that Dobzhansky and Dreyfus found in a Brazilian population of *ananassae* a translocation different from that reported here.

3. According to Freire-Maia, Zanardini and Freire-Maia (1953), this number equals 0.20. The difference is not statistically significant. Brncic (personal communication) found another inversion in Chilean populations besides the two here reported; the mean number of heterozygous inversions per larva was 0.20.

4. Previously cited as *D. montium* in our papers, this species (*kikkawai*) is also polymorphic (very conspicuously so only in females) with respect to the color and pattern of abdominal tergites. The allele for dark pigmentation is dominant over that for light. Experimental populations set up in the laboratory with different initial frequencies of the two forms showed that they tended to change until an equilibrium was reached. Genetic analysis of some populations in this state showed that the three genotypes were present with frequencies in accordance with the Hardy-Weinberg formula. The analysis of samples from 13 different Brazilian populations revealed that the light flies are always more common than the dark ones, occurring nevertheless with statistically significant differences in the genetic composition of some of them. The genetic analysis of about 600 collected males revealed also that the distribution of the three genotypes were in accordance with the Hardy-Weinberg law. (These researches were carried out in collaboration with A. Freire-Maia and W. M. T. Beltrami.)