GENETIC ANALYSIS OF THE ACHAETE-SCUTE SYSTEM OF *DROSOPHILA MELANOGASTER*

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ABSTRACT

Several mutations in the achaete-scute region of Drosophila have been analyzed phenotypically and cytologically. One group of them corresponds to point mutations, another to rearrangements with one breakpoint in this region. *Trans* heterozygotes of the different point mutations or of the different rearrangements show poor complementation or fail to complement; therefore, they could be interpreted as mutations affecting the same gene product. However, left-right inversion recombinants and duplication-deficiency combinations between rearrangements with different cytological breakpoints uncover a complex organization of the achaete-scute region. This region seems to contain several independent achaete and scute functions, as well as a lethal function, arranged as a tandem reverse repeat at both sides of a lethal locus. Since all of the mutants show the same phenotype qualitatively, though different quantitatively, we suggest that these functions are of a reiterative nature. The achaete-scute wild-type condition may well be dependent on a multimeric gene product made of several evolutionary related monomers.

MORPHOGENETIC patterns depend on the spatial distribution of different cell types. To understand the underlying mechanism of pattern formation, we must investigate mutants that alter it. This approach is two-fold. On the one hand, we would like to know the function of the corresponding wild-type alleles of these mutants. On the other hand, we need to know the genetic structure of the loci under consideration and their regulatory relationships.

Among the cuticular pattern mutants of Drosophila, those of the achaete-scute group are characterized by the absence of chaetae in certain positions of the adult cuticular pattern. We will report the analysis of this genetic system in two papers, the present one dealing with its genetic organization and the second with its developmental functions (GARCÍA-BELLIDO and SANTAMARIA 1978).

It was noticed early that different alleles of this group showed different specificities affecting particular groups of chaetae. Phenotype complementation analysis between different mutants distinguished at least two loci, achaete and scute. However, partial complementation was also found between some pairs of alleles of the scute locus; the corresponding heterozygous flies lack the chaetae in the common positions, but differentiate the allele-specific ones (DUBININ 1929, 1933; SEREBROVSKY 1930; AGOL 1931). These authors suggested the existence of

a possible functional subdivision of the scute locus into subgenes (step-alleles), each of which would control the differentiation of chaetae in certain positions.

Genetically, achaete and scute mutants map close together in the tip of the *X* chromosome. The extremely low incidence of meiotic recombination in this region hinders a detailed recombinational analysis of these loci. Thus, although recombination with interchange of lateral markers has been found between two alleles of achaete and scute (DUBININ, SOKOLOV and TINIAKOV 1937), no further analysis has been reported.

The expressivity, *i.e.*, the position specificity of the different scute mutants, varies with temperature (CHILD 1935a,b, 1936; IVES 1939), genetic background and modifiers (CHILD 1935a; STURTEVANT and SCHULTZ 1931; STURTEVANT 1970) and, in the case of some alleles associated with rearrangements, by position-effect variegation (SUTTON 1943). This conditional variation of the specificity of some alleles studied led these authors to postulate that the striking allele specificity results from nonspecific effects of regional or developmental characteristics acting upon different degrees (alleles) of hypomorphism (see GOLDSCHMIDT 1931).

The organizational complexity of the scute locus is, however, supported by the existence of (1) chromosomal rearrangements that have detectably different breakpoints, but which express the scute phenotype, and (2) combinations of these rearrangements that result in a lethal phenotype (MULLER and PROKOFYEVA 1935; RAFFEL and MULLER 1940; see review by MULLER 1955).

The present study suggests that the achaete-scute system corresponds to a "complex locus". It seems to consist of a tandem repeat of reiterative signals, all required for the normal differentiation of nervous elements and coded by segments of DNA spread over at least three salivary chromosome bands.

MATERIALS AND METHODS

The mutant alleles of achaete and scute affect the macrochaetae (called bristles in the classical literature), the microchaetae (called hairs) and the sensillae of the entire body of the fly, as well as the claws of the legs (GARCÍA-BELLIDO and SANTAMARIA 1978). The pattern of effects of the different alleles and genetic combinations will be defined at two levels of expression: the absence of an element corresponding to a position or site (claws and tergites being considered as a unit) in more than 50% of the sites, and in more than 10% of the sides of the flies. Although left and right sides of the same individual derive from imaginal discs separated throughout development, the pattern of suppression is highly correlated, possibly because they share common modifiers and environmental conditions (see RENDEL 1965). The nomenclature of the macrochaetae sites follows that of PLUNKETT (1926). Further details of the adult chaetotaxy and pattern follows FERRIS (1950) (see Figure 1). The viability of the different genetic combinations is expressed as the fraction of individuals of a given combination relative to the genotype of maximal viability of the same cross (a minimum of 200 individuals). Culture vials were screened until no more progeny appeared. Many crosses were made in split bottles so that weak flies could be recovered from the surface of the food.

The mutants and chromosomal rearrangements used will be described in the text. Information relative to their origin, discoverer, and phenotype can be found in LINDSLEY and GRELL (1968). Some of them derived from the collections at Pasadena and Bowling Green. Others were constructed during the course of this work, as explained in the text. Genetic combinations with decreased viability were maintained in stocks balanced over *In(1)dl-49, y Hw* m^2 g^4, *FM6*,

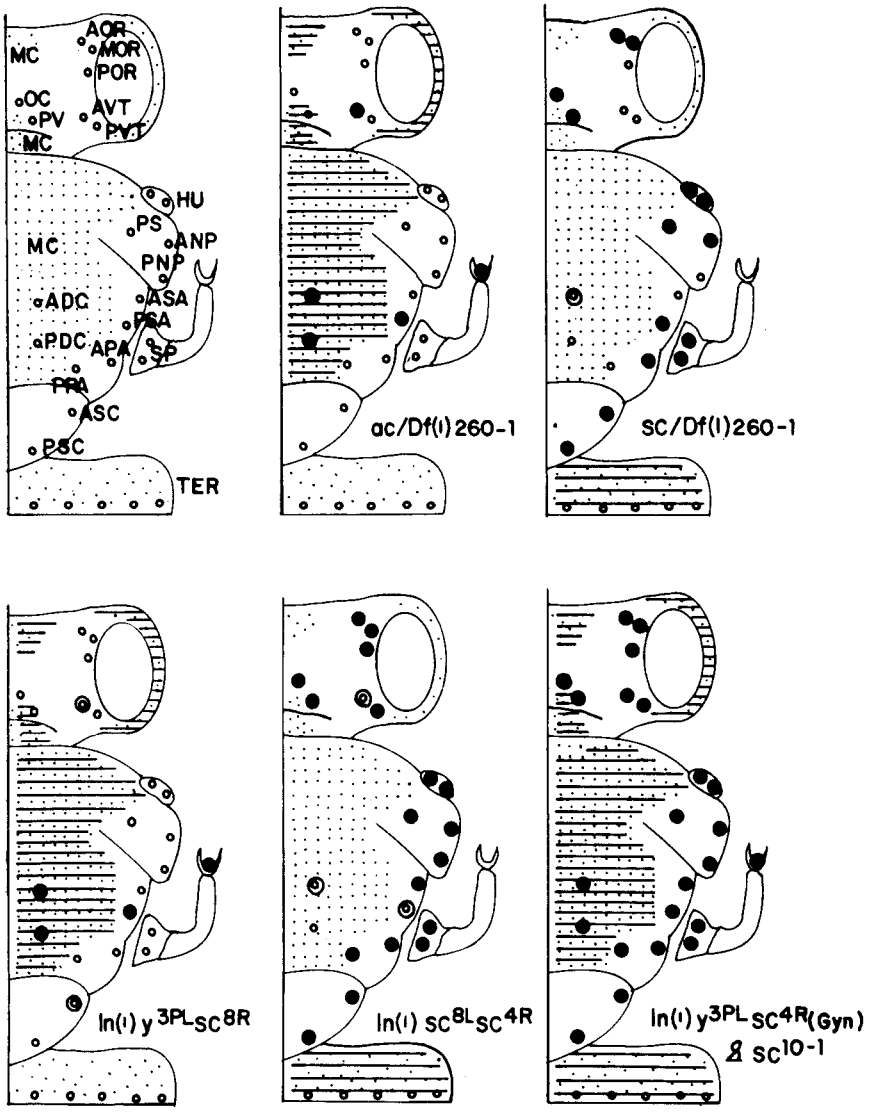

FIGURE 1.—Phenotype of different genetic combinations on chaeta differentiation. In the upper left corner, spatial distribution of the macrochaetae of head (OC: ocelar, VP: postvertical, AVT and PVT: anterior and posterior post-vertical; AOR, MOR and POR: orbitals) thorax (ADC and PCD: dorsocentrals, PS: presutural, HU: humerals, ANP and PNP: notopleurals, ASA and PSA: supraalars, APA and PPA: post-alars, ASC and PSC: scutellars, SP: sternopleurals) and tergites. MC: microchaetae. (For description of the genotypes see text.) Closed circles and bars: suppression in more than 50% of the flies, open circles, in more than 10%.

or attached-X chromosomes. In order to make crosses in which the male was inviable, the Y chromosome present in the stock carried $Dp(1;Y)y^{2}Y^{67g}$ (kindly provided by M. M. GREEN), which covers the scute region. The different stocks used were not made isogenic, but the genetic combinations studied were made in such a way as to minimize possible effects of genetic modifiers. In all experiments, temperature was maintained at 25 $\pm 1°$.

RESULTS

The genetic structure of a locus is always inferred from the behavior, at the phenotypic level, of genetic combinations. We will first describe the phenotypes of point mutations, and later those of chromosomal rearrangements in different genetic combinations. It is our goal to define the extent and organization of the achaete and scute genes in genetic (complementation), as well as in cytogenetic (bands in salivary chromosomes) terms.

The point mutations

Among the numerous reported point mutations of the achaete and scute loci, we have chosen two *ac* alleles and six *sc* alleles for study. They were chosen as representative of different degrees of expression, different specificities and different (spontaneous or induced) origins. It was known for most of them that they are fully recessive in heterozygous females and varied in expressivity in hemizygous males, homozygous females, and in heterozygous combination with genetic deficiencies (AGOL 1932; DUBININ 1933). We have restudied the phenotype of those mutants in (1) hemizygous males arising from an outcross of heterozygous females with wild-type males; (2) in *X/O* males resulting from outcrosses of parental males to *XX/O* females; (3) in homozygous females resulting from backcrosses of mutant males to heterozygous females; and (4) in females heterozygous for the mutant allele and different deficiencies, including *Df(1)260–1*, *Df(1)sc*^{19}, *In(1)y*^{sPL}*sc*^{sR}, *In(1)sc*^{sL}*sc*^{4R} and *In(1)sc*^{4L}*sc*^{9R} (see LINDSLEY and GRELL 1968, and below, for descriptions of these deficiencies).

Table 1 and Figures 1 and 2 provide a general view of the phenotypic characteristics of the different point mutations in different combinations. The data on expressivity and viability are summarized in Table 1. Expressivity is here measured as overall degree (in arbitrary units) of removal of chaetae (sites and frequency) compared to *XY* males. In Figures 1 and 2 the penetrance of suppression (levels of 10 and 50%) for individual sites in the most characteristic genetic combinations is shown. Expressivity is similar in homozygous females and hemizygous males. The only clear exception is *sc*^{sB}, where homozygous females are slightly more extreme than males. Possibly all the mutants studied are dose compensated. It is generally true, also, that expression is more extreme in females heterozygous with deficiencies than in homozygous condition, confirming the observation of AGOL (1932) and DUBININ (1933). This phenomenon is typical of hypomorphic mutations for sex-linked mutants. Phenotypes are slightly more extreme over *Df(1)260–1* than over *Df(1)sc*^{19} (Figure 2). Since *Df(1)260–1* extends more proximally than *Df(1)sc*^{19} and since *T(1;2)sc*^{19} is *sc* in phenotype, we tentatively conclude that *Df(1)sc*^{19} still retains some *sc*$^{+}$ (and *ac*$^{+}$) function (see below). The various point mutants differ with respect to their expressivity in combination with the partial deficiencies *In(1)y*^{sPL}*sc*^{sR}, *In(1)sc*^{sL}*sc*^{4R} and *In(1)sc*^{4L}*sc*^{9R} (Table 1). However, whereas *ac* and *sc*^{sB} are more extreme over *In(1)y*^{sPL}*sc*^{sR}, the rest are more extreme over *In(1)sc*^{sL}*sc*^{4R} and *In(1)sc*^{4L}*sc*^{9R} and, as a rule, more so over the former than over the latter. This complementation analysis suggests that *ac* and *sc*^{sB} are mutants affecting a function present to

TABLE 1

Viability and expressivity of the point mutants in different genetic combinations

Origin	Males		Homozygotes		Females							
	XY		*XX*		*260-1*		*sc*^{19}		Heterozygotes with deficiencies $y^{3PL}sc^{8R}$		$sc^{8L}sc^{4R}$		$sc^{4L}sc^{9R}$	
ac^{1} (spont.)	+*	1.0†	+	1.0	++	0.4	++	0.8	+	0.8	O	0.6	O	0.8
sc^{1} (spont.)	+	1.0	+	1.0	+++	0.4	++	0.3	O	0.6	++	0.6	+	0.6
sc^{2} (X rays)	+	0.5	+	0.1	++	0.1	++	0.1	O	0.8	++	0.8	++	0.4
sc$^{3-1}$ (X rays)	O	1.0	O	0.1		L		L	++	1.0	+++	0.2	++	0.8
sc^{3B} (spont.)	+	1.0	+	1.0	++	0.2	++	0.2	++	1.0	O	0.5	O	1.0
sc^{5} (X rays)	+	1.0	+	1.0	++	0.8	++	0.8	O	1.0	+	0.8	+	1.0
sc^{6} (X rays)	+	1.0	+	1.0	+++	0.4	++	0.8	O	1.0	++	1.0	++	0.8
sc^{D2} (spont.)	+	1.0	+	1.0	+++	0.4	++	0.4	O	1.0	++	0.6	+	0.8
sc^{Ls} (?)	+	1.0	+	1.0	+++	0.8	++	0.9	O	1.0	++	1.0	++	1.0

* Left columns: expressivity (in arbitrary units relative to that of *XY* males, (O): wild type, + — +++ degrees of mutant phenotype).
† Right columns: viability (measured as the fraction of mutant flies relative to the most viable genotype of the same cross). Maximal viability: 1. (In parentheses, the reported origin of the mutation). L: lethal.

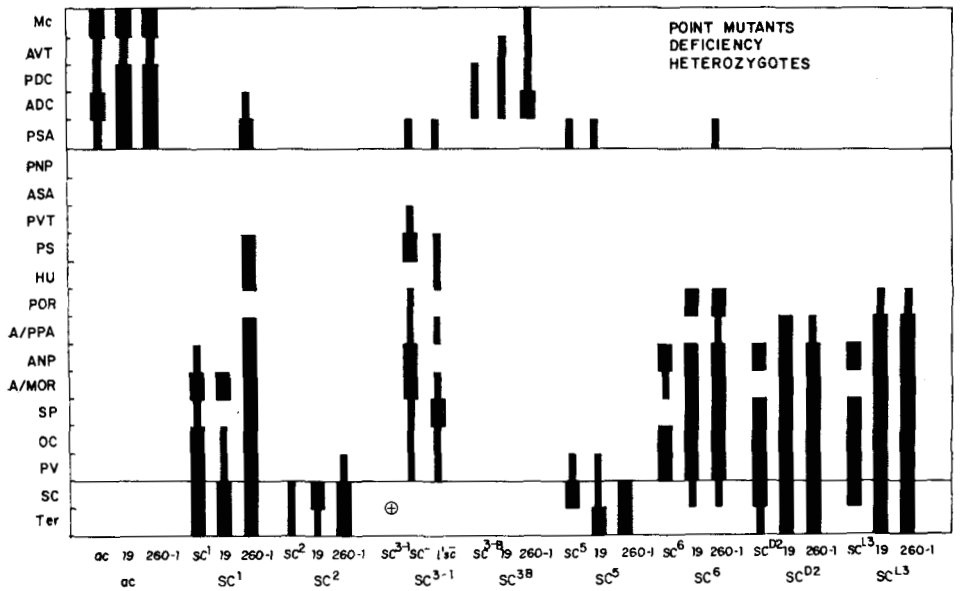

FIGURE 2.—Site positions affected by the different point mutants. Symbolism in ordinates as in Figure 1. Heavy bars: 50% suppression; light bars: 10% suppression. In each group the phenotype of the point mutant in homozygous females (left) and in female heterozygous over *Df(1)sc*^{19} and *Df(1)260-1* (right). In *sc*$^{3-1}$, the females were heterozygous over *sc*$^{-}$ [*In(1)sc*^{8L}-*sc*^{4R}] and over *l'sc*$^{-}$[*In(1)sc*^{4L}*sc*^{9R}] + wild-type.

some extent in *In(1)sc*^{8L}*sc*^{4R} and *In(1)sc*^{4L}*sc*^{9R}. By contrast, the remaining scute alleles studied affect a function partially present in *In(1)y*^{3PL}*sc*^{8R}, and incompletely so in both *In(1)sc*^{8L}*sc*^{4R} and *In(1)sc*^{4L}*sc*^{9R}. In other words, these point mutations do not fully complement with any of the partial deficiencies.

A detailed analysis of the pattern of sites affected by the mutants studied agrees with previous observations (see DUBININ 1933) on the alleles *sc*^{1}, *sc*^{2}, *sc*^{5}, *sc*^{6}. With the inclusion in our analysis of more alleles and the consideration of homozygous females as well as heterozygous deficiency females, it is possible to order the studied mutants into phenotypic groups. In Figure 2, we have plotted a sequence of sites in such a way that the different alleles have a maximal number of affected sites neighboring in the sequence. It is interesting to notice that this seriation is consistent for all the alleles studied. Moreover, the seriation in heterozygous deficiency females includes neighboring sites at both extremes of the sequence of the corresponding homozygous females. This seriation of sites is now similar to the map of the organization of the achaete-scute "basigen" of SEREBROVSKY (1930) and DUBININ (1933). From a consideration of Figure 2, there seem to be four main groups of alleles classified by their site-suppression pattern: *ac*^{1} and *sc*^{3B} (group A, Figure 1); *sc*^{2} and *sc*^{5} (group B); *sc*$^{3-1}$ and *sc*^{6} (group C); and *sc*^{1}, *sc*^{D2} and *sc*^{L3} (group D, Figure 1). Group A affects an "achaete" pattern and group D affects a "scute" pattern, which includes the apparently complementary groups B and C. However, if we consider the pheno-

type of heterozygous deficiency females, there are overlaps in the sites affected by these groups, *i.e.*, between A and D in PSA and between B and C in PV and SC.

This seriation of the different allelic phenotypes (and their phenotypic overlap) was tested in genetic complementation tests (Figure 3). In the heterozygous flies the pattern affected does not correspond to the sites affected in both homozygous individuals. Thus, *ac* does complement with different scutes, including sc^{3B}, which belongs to the same A group; sc^{1} and sc^{D2} or sc^{L3}, all of group D, complement, though poorly; and sc^{2}/sc^{5} (group B) and sc^{3-1}/sc^{6} (group C) largely complement. However, sc^{5}/sc^{6} or sc^{2}/sc^{6}, which correspond to different groups, do not complement, especially in sites of the sc^{6} pattern. These observations are suggestive of dominance relationships, *trans* interactions or polar effects between different alleles (see DISCUSSION). They are also in accord with the observation noted above that the point mutants do not entirely complement with the partial deficiencies. These results agree with the interpretation of DUBININ (1929), and with its more modern statement by STURTEVANT (1970), that the achaete and scute alleles belong to a pseudoallelic system.

The analysis of viability of the different genetic combinations presented in Table 1 suggests that, besides a phenotype of chaetae suppression, the different

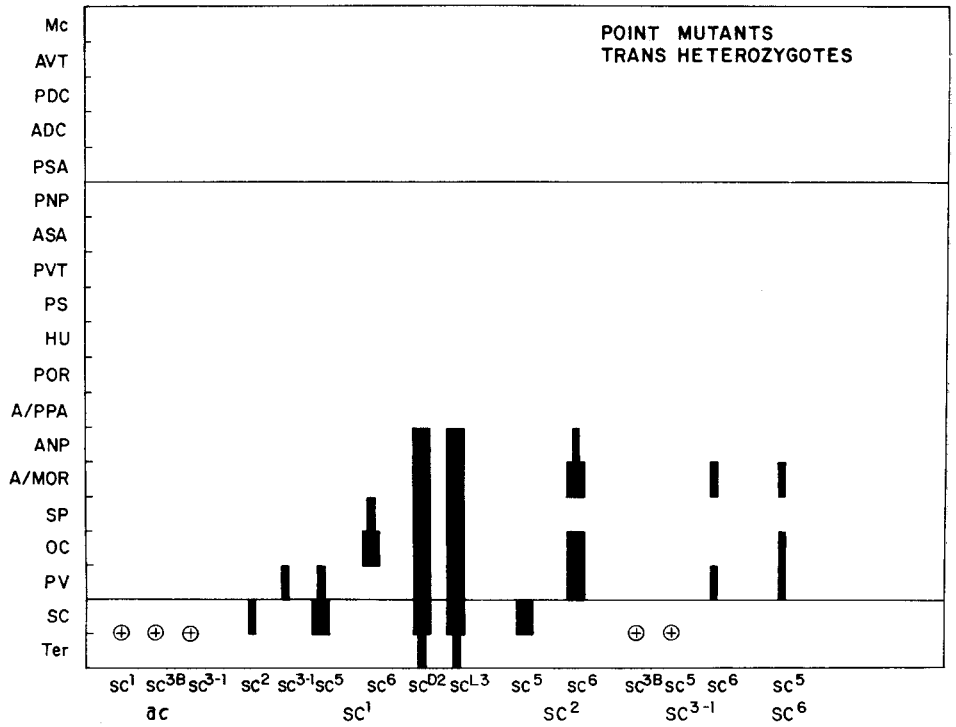

FIGURE 3.—Site positions affected in the *trans* heterozygotes of different point mutants. Same symbolism as in Figure 2.

alleles cause impaired viability. In most alleles the inviability of the different combinations runs parallel with the degree of expressivity for chaetae suppression. However, in sc^{s-1} and, to some extent, in sc^{2} and sc^{sB}, which are characterized by a weak effect on chaetae, the viability of the homozygous females or females heterozygous over deficiency is strongly reduced. In fact, $sc^{s-1}/Df(1)sc^{19}$ and $sc^{s-1}/In(1)y^{sPL}sc^{4R}$ are lethal. It is interesting that in females heterozygous for partial deficiencies, the lower viabilities are shown over $In(1)sc^{sL}sc^{4R}$, except for sc^{2} which is less viable over $In(1)sc^{4L}sc^{sR}$. The existence of these two, not necessarily correlated, components of the scute phenotype will be analyzed below.

Since some of the mutants studied are of X-ray origin, a note of caution should be made whenever we want to explain a complex phenotype in terms of a single mutation. However, it gives us some confidence that the most extreme alleles (ac^{1}, sc^{1} and sc^{D2}) are of spontaneous origin. It is conceivable, however, that the noncorrelated effects on viability and chaeta suppression of sc^{2} and sc^{s-1} might derive from two independent mutational events in the same scute region.

The rearrangements

In contrast with the aforementioned mutations, which do not show cytological abnormalities of the salivary chromosomes, the following (Figure 4) achaete-scute mutants are associated with chromosomal rearrangements. One of the breakpoints (designated here as "left") is in all cases in the region of salivary bands 1B1–1B4 (see below). It might be assumed that, since rearrangement breakpoints represent interruptions in the sequence of DNA, the phenotype

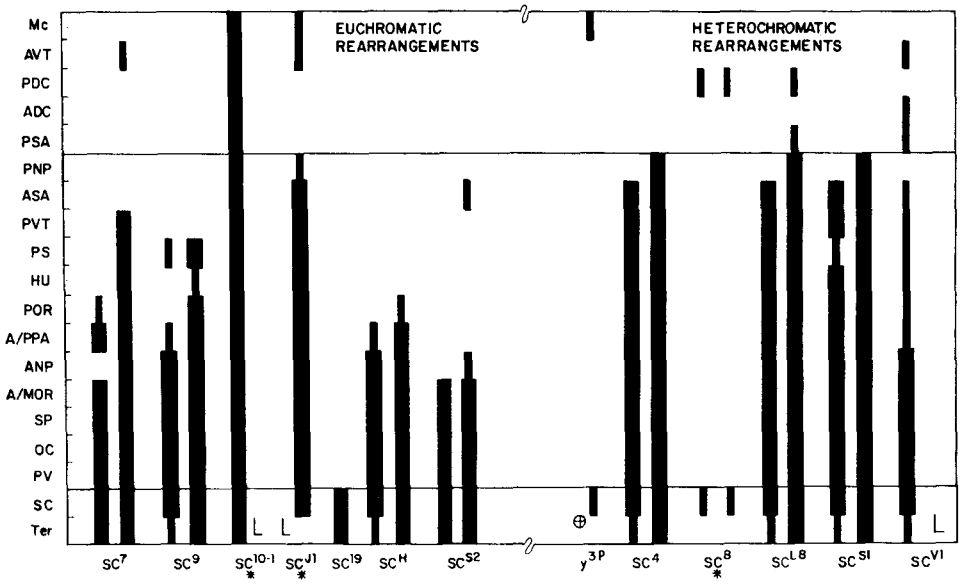

FIGURE 4.—Site positions affected by different rearrangements. In each group the phenotypes correspond to the homozygous females (or hemizygous males, *) (left) or to females heterozygous over $Df(1)sc^{19}$ (right). Same symbolism as in Figure 2.

should be the equivalent to amorphic mutations for the interrupted structural locus. Thus, if the achaete-scute system represents a single function, the phenotypes of all the rearrangements should be identical and maximal. That this is not the case further supports the classical interpretation that the achaete-scute system is functionally complex. Thus, the analysis of these rearrangement mutants should provide information about functional organization (MULLER 1935b). The rearrangements studied are of two classes: those in which the "right" breakpoint is in the euchromatin and those in which it is in the heterochromatin. In the latter case, the phenotype can be originated or modified by position-effect variegation on the adjacent euchromatic regions.

Figure 4 shows the phenotypes of different rearrangements in homozygous females (or in hemizygous males when the females are lethal) and in females heterozygous for the rearrangements and *Df(1)sc^{19}*. In the heterochromatic rearrangements, the phenotype of *X/O* males has been studied in order to evaluate the extent of the phenotype due to variegation. In general, females heterozygous with *Df(1)sc^{19}* are more extreme in phenotype than the corresponding homozygotes, as was true with the point mutants. In this case, however, these differences cannot be explained in terms of hypomorphism of the rearrangement since breakpoints are assumed to generate amorphic mutations. They could result from dosage compensation. Since the phenotype of *X/O* males is not much more extreme than that of *X/Y* males or homozygous females, we tentatively conclude that the phenotype of the heterochromatic rearrangements does not largely result from heterochromatic variegation of intact genes.

It is interesting to note that, on the whole, the phenotypes associated with rearrangements are more extreme than those of point mutations. The phenotype of the homozygous females varies among the different rearrangements (Figure 4), but the affected sites map contiguously in the seriation we constructed to order the point mutations. In the rearrangements, however, the differences in expression are quantitative, extending more-or-less from the bottom of the seriation, corresponding to either group A or D of the point mutants.

An analysis of the *trans* heterozygotes of some of these rearrangements clearly reveals noncomplementation (Figure 5). As a rule, the phenotype of the combinations corresponds to that of the weaker allele, which is another indication that these rearrangements all affect the same function.

The left-right inversion recombinants: The interpretation of the different phenotypes of the rearrangement mutants started with the outstanding work of MULLER (1935b) and MULLER and PROKOFYEVA (1935). They demonstrated that scute or achaete rearrangements can have different breakpoints. This was shown by producing inverted chromosomes having the left region of one inversion and the right region of another. The underlying assumption was that if the breakpoints were genetically different, the reciprocal recombinants would be either duplicated or deficient for the genetic material between the breakpoints. From the phenotype of both reciprocal classes of recombinants, a decision could be made as to whether their breakpoints were different or indistinguishable (RAFFEL and MULLER 1940; see also MULLER 1955). We have repeated some of the combina-

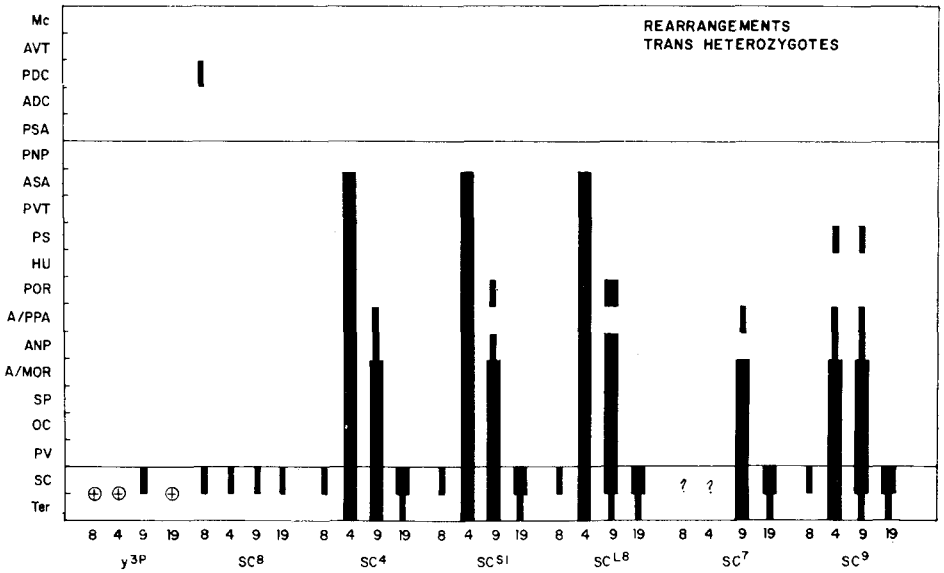

FIGURE 5.—Site positions affected by different rearrangements in *trans* heterozygotes. Same symbolism as in Figure 2. The legends 8, 4, 9, 19 correspond to *In(1)sc*^{8}, *In(1)sc*^{4}, *In(1)sc*^{9}, *T(1;2)sc*^{19}. ?: not studied.

tions (Table 2) and confirmed MULLER's results (see Figure 6). The left breakpoints of *In(1)y*^{3P} and *In(1)sc*^{8} are genetically different, for *In(1)y*^{3PL}*sc*^{8R} is phenotypically *y* and extreme *ac* (MULLER 1935b); whereas, *In(1)sc*^{8L}*y*^{3PR} is *y*$^{+}$ *ac*$^{+}$ and shows a variable Hairy-wing (*Hw*) phenotype in the mesopleura. The same applies to the left breakpoints of *In(1)sc*^{8} and *In(1)sc*^{4}. Here, however, *In(1)sc*^{8L}*sc*^{4R} shows an extreme *sc* but a slight *ac* phenotype. Hemizygous males of this genotype are poorly viable, and after hatching they remain immobile on the food. Homozygous females of this genotype are fully inviable. The left breakpoints of *In(1)sc*^{4}, *In(1)sc*^{L8} and *In(1)sc*^{S1} are genetically similar, for they show the same phenotype in left-right combinations with *In(1)sc*^{9} (RAFFEL and MULLER 1940) and with *In(1)y*^{3P}. *In(1)sc*^{4L} (or *sc*^{S1L}, *sc*^{L8L}) *sc*^{9R} is a lethal combination, and *In(1)y*^{3PL}*sc*^{4R} (or *sc*^{S1R}) is lethal also. However, the former are embryonic lethals, whereas the latter are pupal lethals (GARCÍA-BELLIDO and SANTAMARIA 1978). Their phenotypes differ in other respects, too (GARCÍA-BELLIDO and SANTAMARIA 1978). As expected, *In(1)sc*^{4L}*y*^{3PR} flies are fully viable, *ac*$^{+}$ and *sc*$^{+}$, and only show a weak *Hw* phenotype (Table 2, Figure 6).

These findings are consistent with the interpretation of MULLER (1955) that the known breakpoints of rearrangements in the achaete-scute region subdivide the system into at least three functional units (see Figure 6). Between the left breakpoints of *In(1)y*^{3P} [and *In(1)y*^{4}] and *In(1)sc*^{8} there is an *ac*$^{+}$ function, between those of *In(1)sc*^{8} and *In(1)sc*^{4} [or *In(1)sc*^{S1} or *In(1)sc*^{L8}] there is a *sc*$^{+}$ function, and between those of *In(1)sc*^{4} [or *In(1)sc*^{S1} or *In(1)sc*^{L8}] and *In(1)sc*^{9} there is a function required for viability. The mortality of *In(1)y*^{3PL} *sc*^{4R} (or *sc*^{S1R}) is probably due to the cumulative effect of the lack of *ac*$^{+}$ and *sc*$^{+}$ func-

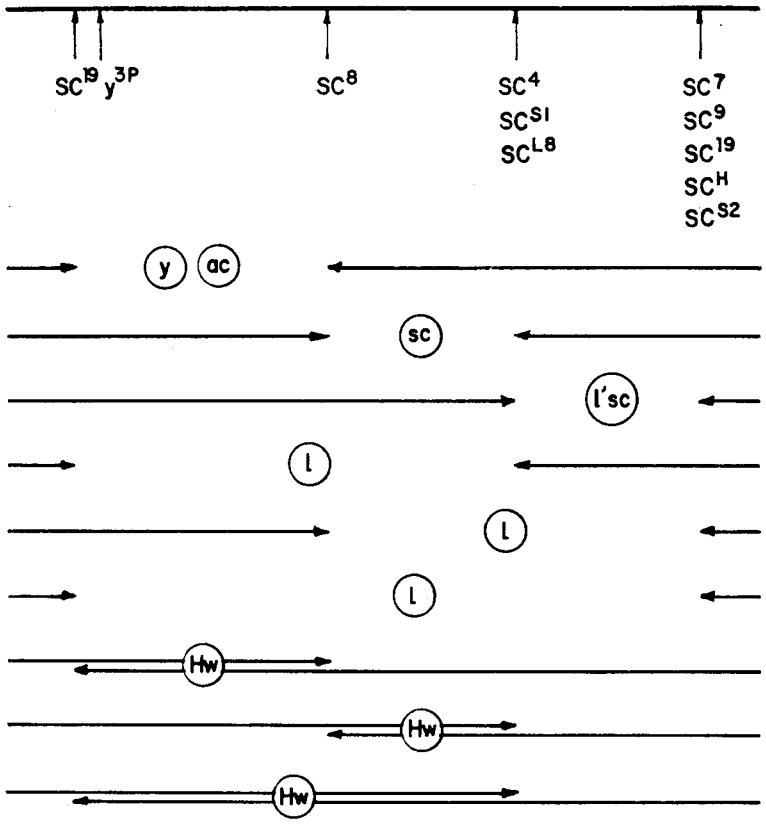

FIGURE 6.—Phenotype of different genetic combinations between left and right elements of inversions and *Df(1)sc*^{19}. Breakpoints indicated by vertical arrows. Empty horizontal spaces: deficiencies. Phenotypes surrounded by a circle.

TABLE 2

Viability and phenotype of males of different left-right inversion recombinants

Genetic constitution *In(1)*	Viability* %	Phenotype *ac*	*sc*	*Hw*	*l'sc*
$y^{3PL}\ sc^{8R}$	0.60	—	+	+	+
$sc^{8L}\ y^{3PR}$	1.00	+	+	—	+
$sc^{8L}\ sc^{4R}$	0.10	±	—	+	+
$sc^{4L}\ sc^{8R}$	1.00	+	+	—	+
$sc^{4L}\ sc^{9R}$	0.00	(+)	(—)	+	—
$sc^{S1L}\ sc^{9R}$	0.00	?	?	+	—
$sc^{L8L}\ sc^{9R}$	0.00	?	?	+	—
$y^{3PL}\ sc^{4R}$	0.00	(—)	(—)	+	+
$y^{3PL}\ sc^{S1R}$	0.00	(—)	(—)	+	+
$sc^{4L}\ y^{3PR}$	1.00	+	+	—	+
$sc^{8L}\ sc^{9R}$	0.00	(±)	(—)	+	—
$y^{3PL}\ sc^{9R}$	0.00	—	—	+	—

+: wild type and —: mutant (*ac*, *sc* *Hw* or *l'sc*) phenotype. *l'sc*: lethal of scute. Viability measured as in Table 1. In parentheses, the phenotype seen in male spots in gynandromorphs (see GARCÍA-BELLIDO and SANTAMARIA 1978).

tions. This is confirmed by the very poor viability of sc^{10-1} flies, partially deficient (SCHULTZ, quoted in LINDSLEY and GRELL 1968 and see below) for sc^+ and for ac^+. Homozygous sc^{10-1} females are, in fact, lethal.

The inviability of $In(1)sc^{4L}$ (or sc^{S1L} or sc^{L8L}) sc^{9R} cannot be explained in terms of variegation because the right breakpoint of $In(1)sc^9$ is euchromatic. Although $In(1)sc^4$, $In(1)sc^{L8}$ and $In(1)sc^{S1}$ have right breakpoints in heterochromatin, any suppression of function (variegation) distal to their left breakpoints is compatible with viability, as we have seen. The lethality of $In(1)sc^{4L}sc^{9R}$ was shown by MULLER (1935b) not to derive from the duplication of the euchromatic region between the right breakpoint of $In(1)sc^9$ and the centromere, because $Dp(1;2)sc^{19}$ (containing only the *sc* system) renders $In(1)sc^{4L}sc^{9R}$ viable. The function lacking in the deficiencies (and similar ones) was called "lethal of scute" (*l'sc*) by MULLER.

The discovery that the achaete-scute system can be physically subdivided into units is confirmed by the complementation analysis of females heterozygous for intercalary deficiencies. (Table 3; MULLER and PROKOFYEVA 1935; MULLER 1955). Thus, deficiencies proximal to the left breakpoint of $In(1)sc^4$ (or $In(1)sc^{L8}$ or $In(1)sc^{S1}$ are viable over deficiencies distal to these breakpoints, *i.e.*, $In(1)sc^{4L}sc^{9R}/In(1)sc^{8L}sc^{4R}$ or $In(1)sc^{4L}sc^{9R}/In(1)y^{3PL}sc^{4R}$ females are viable although *sc* or *ac* and *sc*, respectively, in phenotype. Similarly, heterozygotes between deficiencies proximal and distal to the breakpoint of $In(1)sc^8$; *i.e.*, $In(1)sc^{8L}sc^{4R}/y^{3PL}sc^{8R}$ or $In(1)sc^{8L}sc^{9R}/y^{3PL}sc^{8R}$ are viable and phenotypically *ac*. The *ac* or *sc* phenotype shown by these heterozygous females corresponds to the phenotype of the common breakpoints (Figure 5). This finding suggests that, although these deficiencies complement for the chaeta phenotype and viability, their breakpoints create an insufficiency that cannot be rescued by any other region of the system.

This conclusion is supported by the study of complementation between pairs of inversions or translocations with different breakpoints (Figure 5). All the combinations are viable, but phenotypically they are more extreme the stronger are the individual scute phenotypes of the combination. There is no case of phenotypic complementation between alleles. We have seen a similar lack of complementation between point mutants. However, in the case of rearrangements with cytologically different breakpoints, it may seem surprising to find a lack of complementation. These observations suggested that we attempt a more detailed analysis of the breakpoints of the different rearrangements with the aim of defining the genetic functions affected by or located between them.

Duplication-deficiency combinations: The left-right test is limited to inversions and in most cases to those that do not create inviable aneuploidy. Thus, we had to resort to studying the functional organization of the achaete-scute system by making use of available or newly constructed terminal duplications and deficiencies. The approach consisted of studying, in males deficient for different segments of the tip of the *X* chromosome, the phenotype resulting from adding different duplications.

As terminal deficiencies, we used $Df(1)svr$, $Df(1)260\text{–}1$, $Df(1)sc^H$ [aneuploid segregant from $T(1;4)sc^H$], $Df(1)sc^{S2}$ [aneuploid segregant from $T(1;2)sc^{S2}$],

TABLE 3

Viability and phenotype of females heterozygous for different deficiencies

	$In(1)_{y^{3PL}\ sc^{9R}}$	$In(1)_{sc^{8L}\ sc^{9R}}$	$In(1)_{sc^{4L}\ sc^{9R}}$	$In(1)_{y^{3PL}\ sc^{4R}}$	$In(1)_{sc^{8L}\ sc^{4R}}$	$In(1)_{y^{3PL}\ sc^{8R}}$	$Df(1)_{sc^{10-1}}$	$Df(1)_{sc^{19}}$	$Df(1)_{sc^{8}}$
$Df(1)sc^{10-1}$	L	L	0.5 *sc*	L	L	0.1 *ac*	L	L	0.1 *ac*
$In(1)y^{3PL}\ sc^{9R}$	L			L			L	L	0.1 *ac*
$In(1)sc^{8L}\ sc^{9R}$		L		L	L	0.2 *ac sc*		L	0.1 *ac*
$In(1)sc^{4L}\ sc^{9R}$			L	0.1 *ac sc*	0.3 *sc*	0.5 *sc*	L	L	1.0 *sc*
$In(1)y^{3PL}\ sc^{4R}$				L	L			L	0.1 *ac*
$In(1)y^{3PL}\ sc^{S1R}$	L			L	L			L	0.1 *ac*
$In(1)y^{8L}\ sc^{4R}$					L	0.9 *ac*	L	L	1.0 *ac*
$In(1)y^{3PL}\ sc^{8R}$						0.9 *ac*	0.1 *ac*	0.2 *ac*	0.8 *ac*

Viability expressed as in Table 1. L: lethal.

Df(1)sc^{VI} [recombinant of *In(1LR)sc^{VI}*], and *Df(1)sc^{8}*. *Df(1)sc^{4}*, *Df(1)sc^{L8}*, and *Df(1)sc^{S1}* were constructed as *Df(1)sc^{8L}sc^{4R}*, or *Df(1)sc^{8L}sc^{L8R}* and *Df(1)sc^{8L}sc^{S1R}*, respectively. As intercalary deficiencies of this region, we have used the *In(1)LR* recombinants mentioned above, *Df(1)sc^{19}* [aneuploid segregant of *T(1;2)sc^{19}*], and *Df(1)sc$^{10-1}$*. As terminal duplications, we employed *Dp(1;f)24*, *Dp(1;2)sc^{S2}*, *Dp(1;4)sc^{H}*, *Dp (1;f)sc$^{7.2}$* (received from I. OSTER and found by me to contain neither *cv*+, *ec*+, nor *car*+ so that possibly its left breakpoint corresponds to that of the inversion *In(1)sc^{7}*, but now adjacent to the centromeric heterochromatin), *Dp(1;Y)sc^{S1}*, *Dp(1;Y)sc^{8}*, *Dp(1;3)sc^{J4}*, *Dp(1;Y)sc^{VI}* (RIPOLL and GARCÍA-BELLIDO 1973) and *Dp(1;Y)l(1)J1*+. Finally *Dp(1;2)sc^{19}* was used as an intercalary duplication.

Table 4 and Figures 7 to 9 show the phenotype (chaeta pattern and viability) of some deficiency-duplication combinations. In Table 4 the duplications and deficiencies are ordered from more complementing (left or top) to less complementing (right or bottom). Figure 10 shows a so-called "phenotypic map" based in these results. We assume that the more functional overlap there is between the duplication and the deficiency, the more wild type the phenotype will be, and

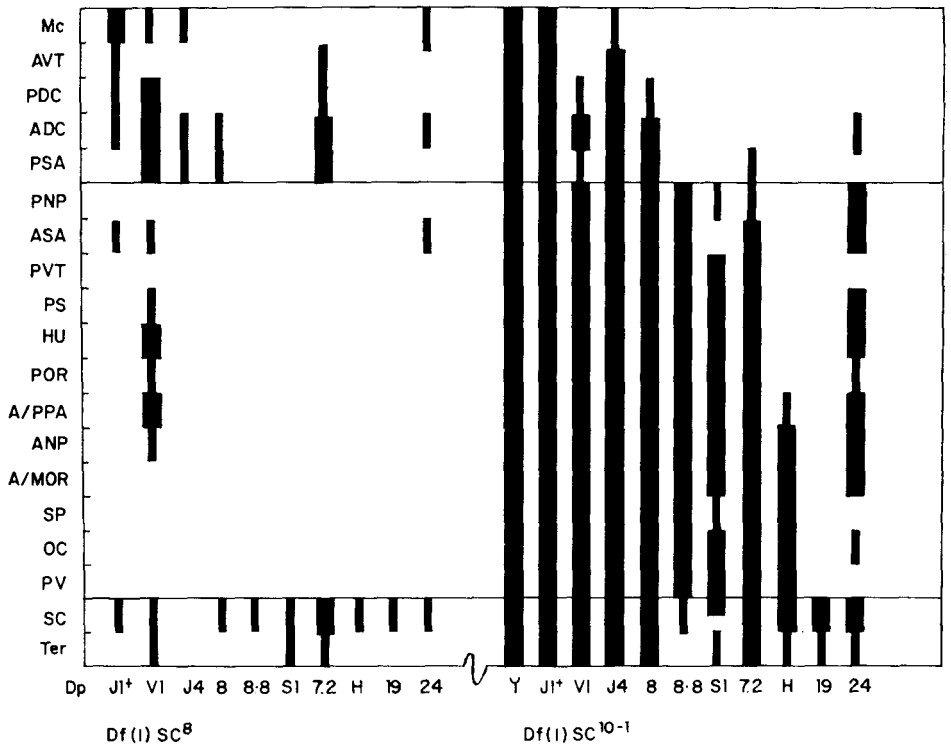

FIGURE 7.—Site positions affected by different duplication (*Dp*)-deficiency (*Df*) combinations. Duplications: *J1*+: *Dp(1;Y)J1*+; *V1*: *Dp(1;Y)sc^{V1}*; *J4*: *Dp(1;3)sc^{J4}*; 8: *Dp(1;Y)sc^{8}*; 8–8: *Dp(1;Y) sc^{8}*, *sc^{8}*; S1: *Dp(1;Y)sc^{S1}*; 7.2: *Dp(1;f)sc$^{7.2}$*; H: *Dp(1;4)sc^{H}*; 19: *Dp(1;2)sc^{19}*; 24: *Dp(1;f)24*. Other symbolism as in Figure 2.

TABLE 4

Viability and phenotype of deficiency-duplication males

Deficiency	Duplication												
	$Dp(1;f)101$	$Dp(1;f)24$	$Dp(1;2)sc^{19}$	$Dp(1;2)sc^{8l2}$	$Dp(1;4)sc^{H}$	$Dp(1;f)sc^{7.2}$	$Dp(1;Y)sc^{81}$	$Dp(1;Y)sc^{8}$	$Dp(1;Y)sc^{V1}$	$Dp(1;3)sc^{J4}$	$Dp(1;Y)l^{J1+}$	$Dp(1;Y)sc^{8}Ysc^{8}$	—
Df(1)svr	1.0	L		L	L								L
Df(1)260-1	1.0	0.1 *ac sc*	L* (*sc*)	L	L† (*sc*)	L							L
$Df(1)sc^{19}$	1.0	0.8 *ac sc*	1.0 *sc*	0.8 *sc*	0.8 *sc*	0.4 *ac sc*	L	L	L	L			L
$Df(1)sc^{S2}$		0.2 *sc*	0.3 *sc**	0.9 *sc*	0.3 *sc*	0.3 *ac sc*	L	L					L
$Df(1)sc^{H}$		1.0 *sc*	0.8 *sc**	0.3 *sc*	0.9 *sc*	0.3 *ac sc*	L	L					L
$Df(1)sc^{V1}$					0.1 *sc*	0.1 *ac sc*	L	L	0.1 *ac sc*	L			L
$Df(1)sc^{4}$		0.5 *sc*	1.0 *sc**		0.3 *sc*	0.6 *ac sc*	0.9 *sc*	0.1 *ac sc*	0.1 *ac sc*	0.1 *ac sc*	L	L	L
$Df(1)sc^{L8}$					0.3 *sc*		0 5 *Hw sc*	0.1 *ac sc*		0.2 *ac sc*			L
$Df(1)sc^{8}$		0.7 *ac sc*	1.0 *sc**		1.0 *sc*	0.5 *ac sc*	1.0 *Hw sc*	1.0 *sc*	0.2 *ac sc*	1.0 *ac*	0.3 *ac*	1.0 *Hw*	L
$Df(1)sc^{10-1}$		1.0 *ac sc*	0.4 *sc*		1.0 *sc*	0.5 *ac sc*	0.4 *sc*	0.1 *ac sc*	0.2 *ac sc*	0.1 *ac sc*	0.4 *ac sc*	0.4 *sc*	0.2 *ac sc*
$In(1)y^{3PL}\ sc^{9R}$	1.0		0.1 *sc**	0.1 *sc*	0.1 *sc*		L	L					L
$In(1)sc^{8L}\ sc^{9R}$			0.1 *sc*		0.1 *sc*		L					L	L
$In(1)sc^{4L}\ sc^{9R}$		1.0 *sc*	0.5 *sc*		0.1 *sc*	0.1 *sc*	L	L	L	L		L	L
$In(1)y^{3PL}\ sc^{4R}$			1.0 *sc*		1.0 *sc*		1.0 *sc*	0.3 *ac sc*		0.1 *ac sc*	L		L
$In(1)y^{3PL}\ sc^{S1R}$			1.0 *sc*		0.5 *sc*		0.5 *sc*	0.1 *ac sc*	0.1 *ac sc*	0.2 *ac sc*	L	0.1 *ac sc*	L
$In(1)sc^{8L}\ sc^{4R}$		1.0 *sc*	0.8 *sc*		0.8 *sc*		0.5 *sc*	0.1 *sc*	0.1 *ac sc*	0.1 *ac sc*	L	L	0.1 *ac sc*
$In(1)y^{3PL}\ sc^{8R}$			0.4 *sc*		0.4 *sc*						0.5 *ac sc*		0.6 *ac*

Symbolism as in Table 3.
* These males carried beside $Dp(1;Y)sc^{8}$.
† Pupal lethal.

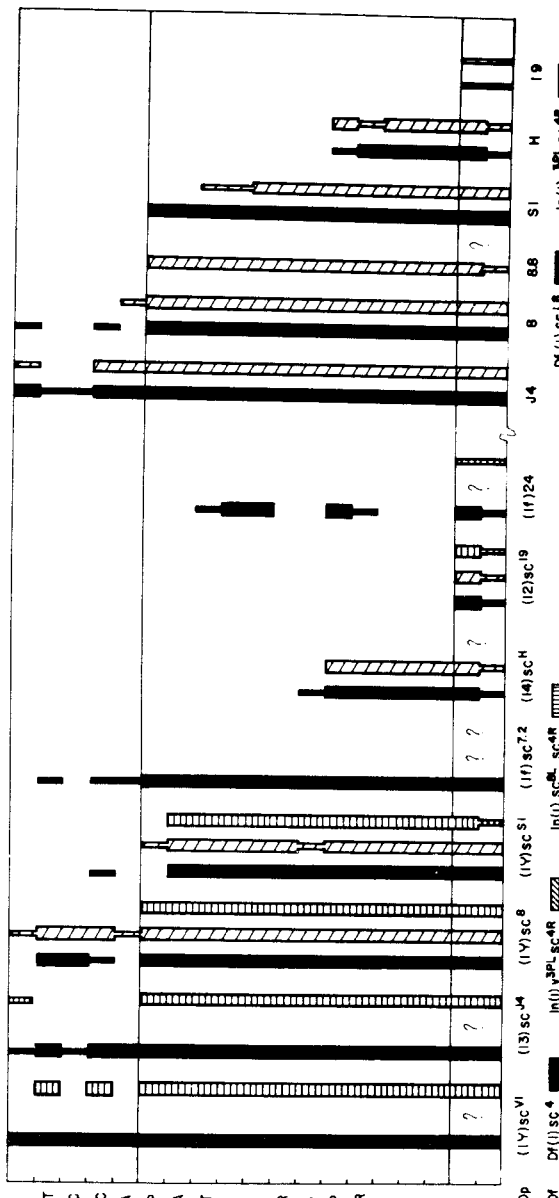

FIGURE 8.—Site positions affected by different duplication (*Dp*)—deficiency (*Df*) combinations. Same symbolism as in Figures 2 and 7. ?: combination not studied.

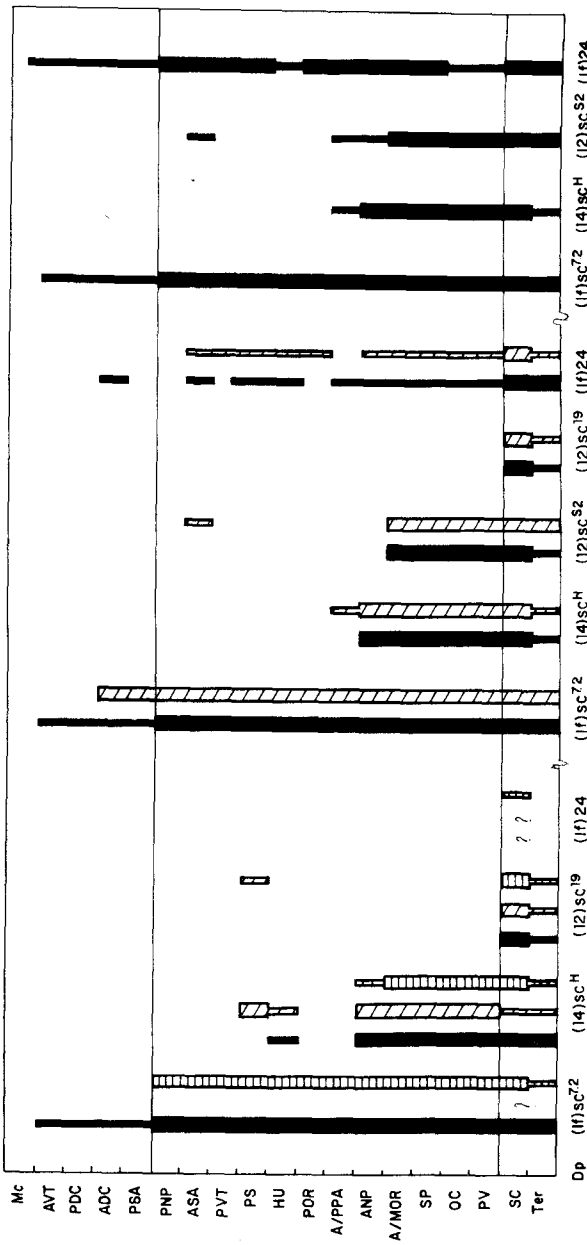

FIGURE 9.—Site positions affected by different duplication (*Dp*)—deficiency (*Df*) combinations. Same symbolism as in Figures 2 and 7.

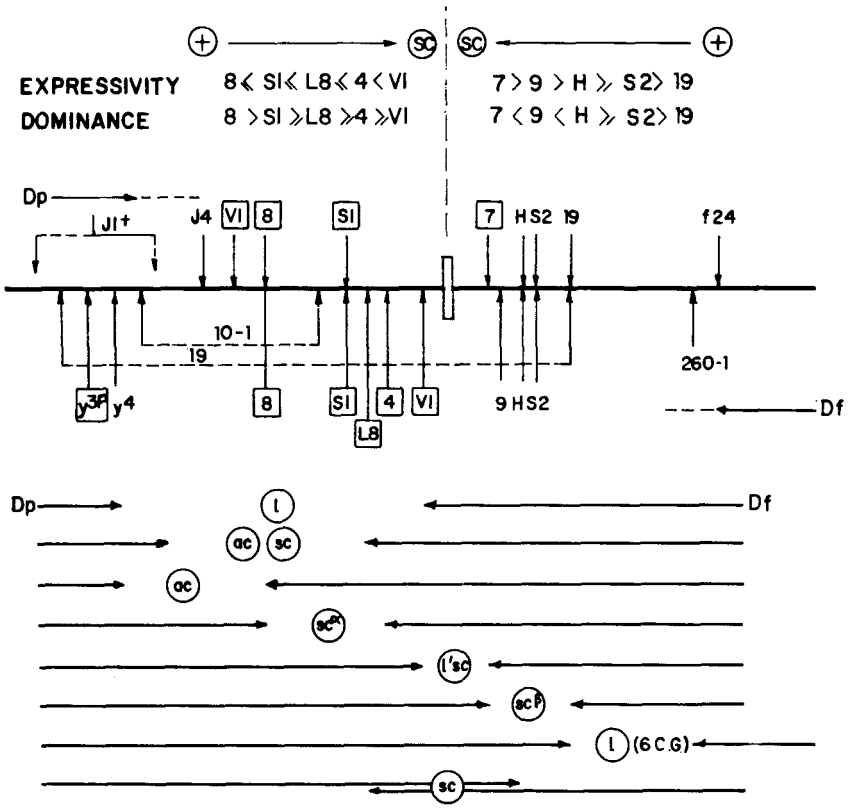

FIGURE 10.—Phenotypic map of different rearrangements in the achaete-scute region. Expressivity and dominance: seriation from less to more scute of the different rearrangements with breakpoints to the left or to the right of lethal of scute. Vertical arrows: site of the breakpoint of rearrangements of different extent [duplication (*Dp*) or deficiency (*Df*) element] inferred from the phenotype of combinations with other deficiencies and duplications. Rearrangements in contact with heterochromatin in squares. Horizontal spaces: phenotype (in circles) of the duplication-deficiency combinations. CG: lethal complementation groups. Symbolism as in Figures 7 to 9.

contrastingly, the more extensive the functional gap between duplication and deficiency, the more extreme the mutant phenotype. Thus, by taking into consideration the resulting phenotypes, we can deduce a "genetic breakpoint map". If the pattern of chaeta suppression is quantitatively different in the different combinations, we can define the genetic functions present between breakpoints. The cytogenetic data (see below) should support the inferred genetic breakpoints.

Dp(1;f)101 covers, phenotypically and cytologically, *Df(1)svr* and all deficiencies distal to it. *Dp(1;f)24*, believed by MULLER (1932) to extend up to scute, actually covers *Df(1)260–1* and, therefore, must extend beyond it. The fact that *Dp(1;f)24* heterozygous with *Df(1)260–1* or with more terminal deficiencies exhibits a scute (and slight achaete) phenotype can be explained either by assuming variegation of scute due to the proximity of the locus to centromeric

heterochromatin, or that the duplication is mutant for scute. The fact that the phenotype is variable and more extreme in *X/O* males supports the first interpretation. This presumed variegation, however, must extend over at least two lethal complementation groups between the scute system and the breakpoint of *Df(1)260–1* (see below) and if the achaete phenotype is due to variegation, it must extend over *l'sc* as well. *Dp(1;2)sc*^{19} was genetically shown by MULLER (1935a) to cover all the recombinational deficiencies created with inversions y^{3P} and sc^{9} (Figures 7 to 9). Thus, it carries y^{+}, ac^{+}, $l'sc^{+}$ and (partially) sc^{+} functions. The study of this duplication over the terminal deficiencies (in males carrying *Dp(1;Y)sc*^{8}) corroborates that interpretation. Since *Dp(1;2)sc*^{19} does not cover *Df(1)260–1*, its right breakpoint must be to the left of that of *Df(1)260–1* deficiency. The fact that all these combinations show a *sc* phenotype confirms again that there is no qualitative complementation between *sc* rearrangements. There are, however, quantitative differences in the scute phenotype, depending on the genetic combinations created by the duplication-deficiencies (Table 4 and Figures 7 to 9). Thus *Dp(1;2)sc*^{S2}*/Df(1)sc*^{19} is phenotypically more extreme than the reciprocal *Dp(1;2)sc*^{19}*/Df(1)sc*^{S2}; *Dp(1;Y)sc*^{8} combination. This finding suggests that the right breakpoint of *T(1;2)sc*^{19} is to the right of the left breakpoint of *T(1;2)sc*^{S2} and that the left breakpoint of *T(1;2)sc*^{S2} is to the right of *l'sc*. In fact, *Dp(1;2)sc*^{S2}*/In(1)y*^{3PL}*sc*^{9R} is viable. It is, as expected, phenotypically *sc*, but more so than *Dp(1;2)sc*^{19}*/In(1)y*^{3PL}*sc*^{9R}, confirming the assumption that the order of breakpoints is sc^{9}, sc^{S2}, sc^{19}. Following similar considerations, it is possible to seriate the breakpoints of the rearrangements to the right of *l'sc*. All the duplication-deficiencies constructed with *T(1;2)sc*^{19}, *T(1;2)sc*^{S2}, *T(1;4)sc*^{H}, *Dp(1;f)sc*$^{7.2}$ and deficiency sc^{9} [including *In(1)y*^{3PL}*sc*^{9R}] are viable, though variable in phenotype depending on the duplication and deficiency elements used in the combination. However, the combinations are consistently more extreme, the farther to the left is the assumed breakpoint of the duplication element and the farther to the right is that of the deficiency element (Figure 10). The phenotype of combinations with breakpoints close together is more similar to the phenotype of their rearrangements in hemizygous males. When the duplication element overlaps the deficiency, the phenotype is that of the rearrangement of the duplication element. The phenotype of these duplication-deficiencies is *sc* only. The only exceptions are those having *Dp(1;f)sc*$^{7.2}$ as the duplication element, which show, besides, a clear but variable *ac* phenotype. This *ac* expression is more extreme in *X/O* males, thus, possibly reflecting variegation for the genetic functions to the left of the breakpoint now in proximity to the centric heterochromatin. The viability of all these combinations is low. This is particularly so in combination with deficiencies for *l'sc* (Table 4), which suggests that *Dp(1;f)sc*$^{7.2}$ also variegates for this function. All the studied rearrangement breakpoints that behave as though they were to the right of *l'sc* are euchromatic.

The constructed seriation of breakpoints is the same as the seriation produced by comparing the phenotypes of the rearrangements (Figure 10). The rearrangements with more extreme phenotypes correspond to breakpoints closer to *l'sc*, and phenotypes become weaker the farther to the right their breakpoints are. The

dominance relationships in females heterozygous for the rearrangements are consistent with the findings of duplication-deficiency males. The phenotype of the rearrangement heterozygote corresponds to that of the more nearly wild-type element, namely that one that has the breakpoint farther to the right (Figure 5).

Based on the phenotype of the duplication-deficiency combinations, the proposed seriation of breakpoints of rearrangements can be mapped (Figure 10). The strength of the scute phenotype of adjacent genetic gaps compared with the phenotype of the corresponding rearrangements suggests that sc^{7} and sc^{9} correspond to the same genetic breakpoint, and sc^{S2} and sc^{H} possibly have identical breakpoints. It is interesting that all the rearrangements and all the created genetic gaps to the right of *l'sc* affect the same seriation of chaetae (Figure 7). Their phenotypes extend, to different degrees, from the bottom of the site seriation (see DISCUSSION).

The existence of a "lethal of scute" was postulated by MULLER (1935a), based on the behavior of certain left-right inversion recombinants. Its existence is operationally confirmed by the behavior of certain duplication-deficiency combinations. Whereas deficiencies such as $Df(1)sc^{4}$, $Df(1)sc^{L8}$, $Df(1)sc^{V1}$, and $Df(1)sc^{8}$ can be rescued by duplications whose breakpoints are to the right of $In(1)sc^{9}$, the reciprocal duplication-deficiency (such as $Df(1)sc^{S2}/Dp(1;Y)sc^{8}$) combinations are not viable (Table 4).

Considerations similar to those used to analyze rearrangements with breakpoints to the right of *l'sc* make it possible to map the rearrangement breakpoints to its left (Table 4, Figures 8 and 9). Since $Dp(1;Y)sc^{S1}$, $Dp(1;Y)sc^{8}$ and $Dp(1;Y)sc^{V1}$ are heterochromatic rearrangements, it is difficult to infer their phenotypic breakpoints. It is possible that the genetic functions present in them, being inactivated by variegation, will give us breakpoints spuriously shifted to the left. This is very probably the case with $Dp(1;Y)sc^{V1}$, which does not cover the lethality of $In(1)sc^{4L}sc^{9R}$ nor that of $Df(1)sc^{4}$, but this duplication over $Df(1)sc^{8}$ or $Df(1)sc^{V1}$ is viable, although strongly *ac* and *sc*. Thus, the $In(1)sc^{V1}$ breakpoint can be mapped close to the left of *l'sc*, but exposed to variegation on both sides of the breakpoint, due to the adjacent centromeric heterochromatin of the right arm of the *X*. In fact, this inversion variegates strongly for *y*. $Dp(1;Y)sc^{S1}/Df(1)sc^{4}$ or $Dp(1;Y)sc^{S1}/Df(1)sc^{L8}$ are very similar in phenotype to the rearrangements sc^{4}, sc^{L8} or sc^{S1} in males, $Dp(1;Y)sc^{S1}/Df(1)sc^{4}$ being slightly stronger than $In(1)sc^{4}$ males (Figure 8). The phenotypes of these deficiencies with $Dp(1;Y)sc^{S1}$ is *sc* only. The same deficiencies, sc^{4} and sc^{L8}, are viable in males carrying $Dp(1;Y)sc^{8}$ or $Dp(1;3)sc^{J4}$ (but not with $Dp(1;Y)lJ1^{+}$) and are both *sc* and *ac* in phenotype. They are more extreme in phenotype and inviability with $Dp(1;Y)sc^{J4}$ than with $Dp(1;Y)sc^{8}$. This inviability is possibly associated with the extreme accumulative effect of *ac* and *sc* phenotypes. As we remember, $In(1)y^{3PL}sc^{4R}$ is lethal, and even $In(1)sc^{8L}sc^{4R}$ is inviable in homozygous females. The lethality of these genotypes is in the pupal period (GARCÍA-BELLIDO and SANTAMARIA 1978), quite different from the lethality of *l'sc* combinations. $Df(1)sc^{10-1}$ males are strongly *ac* and *sc* but viable. Thus, possibly, the right breakpoint of $Df(1)sc^{10-1}$ is different from the left ones of either sc^{L8}, sc^{4} or sc^{S1}.

Its left breakpoint, on the other hand, must be to the left of that of *Dp(1;Y)sc*^{8} and *Dp(1;3)sc*^{J4} because, in their combination, the *ac* chaetae pattern (not the *sc* one) is considerably rescued (Figure 9). It is even more wild type if *Dp(1;Y)* carries two *sc*^{8} duplications [*Dp(1;Y)sc*^{8}, *sc*^{8}]. From these consideration, we could conclude that the left breakpoint of *Dp(1;3)sc*^{J4} is farther to the left than of that of *Dp(1;Y)sc*^{8}. This, in turn, would suggest a subdivision of the *ac* gene. Alternatively, its reduced *ac*$^{+}$ function could result from variegation due to its breakpoint being in the telomeric region of the tip of chromosome *3L*. A similar uncertainty arises in the study of the genetic extent of *Dp(1;Y)lJ1*$^{+}$. MULLER (1954) obtained it as an assumed deletion of part of *Dp(1;Y)sc*^{8} that had lost *ac*$^{+}$ and *y*$^{+}$ functions. It is remarkable that *Dp(1;Y)lJ1*$^{+}$ increases the viability of *Df(1)sc*$^{10-1}$, but does not rescue its *ac* phenotype (Table 4). Thus, it possibly carries some *ac*$^{+}$ function and its *y* phenotype is due to mutation, rather than to deletion. *Dp(1;Y)lJ1*$^{+}$*/Df(1)sc*^{8} is viable and extreme achaete, phenotypically. These males show additionally necrotic leg joints. Thus, between the breakpoints of *Dp(1;Y)lJ1*$^{+}$ and of *Df(1)sc*^{8}, there is no genetic function incompatible with viability.

The left breakpoint of *T(1;2)sc*^{19} is probably to the left of the left breakpoints of *In(1)y*^{3P} and *In(1)y*^{4} because *Dp(1;2)sc*^{19} carries *y*$^{+}$. Between its left breakpoint and that of *Df(1)sc*^{8}, there is no lethal function because *Df(1)sc*^{8}*/Df(1)sc*^{19} females are viable, although phenotypically *y* and *ac* (Table 2).

The discussed seriation of breakpoints of duplication and deficiencies to the left of *l'sc* is consistent with a seriation of the phenotypes of the homozygous rearrangements. Those to the left are *ac* in phenotype; those to the right are *sc*, being more extreme the farther to the right the inferred breakpoint is (Figure 10). The dominance relationships in heterozygous females follow the reverse seriation: left breakpoints are dominant over right breakpoints. It is interesting to note that these seriations are opposite polarity to those found for rearrangements and breakpoints to the right of *l'sc*. Moreover, between the breakpoints to the right of *l'sc*, genetic gaps produce quantitatively different *sc* phenotypes, while between those to the left of *l'sc*, both *ac* and *sc* phenotypes are qualitatively as well as quantitatively different.

The lethal of scute

The foregoing discussion suggests that the scute system is organized as a mirror-image duplication at both sides of the lethal of scute, with stronger scute phenotypes being associated with rearrangement breakpoints closer to *l'sc* (Figure 10). It is therefore surprising that there is no phenotypic complementation between rearrangements within both regions, or between them. RAFFEL and MULLER (1940) and MULLER (1955) noted that rearrangements with breakpoints to the right of *l'sc* were always euchromatic; rearrangement breakpoints to the left were heterochromatic. They speculated that heterochromatic rearrangements with breakpoints to the right would variegate for *l'sc* and therefore could not be isolated. This suggestion does not explain why rearrangements to the left are heterochromatic (with the exceptions of the breakpoints of *Df(1)sc*$^{10-1}$

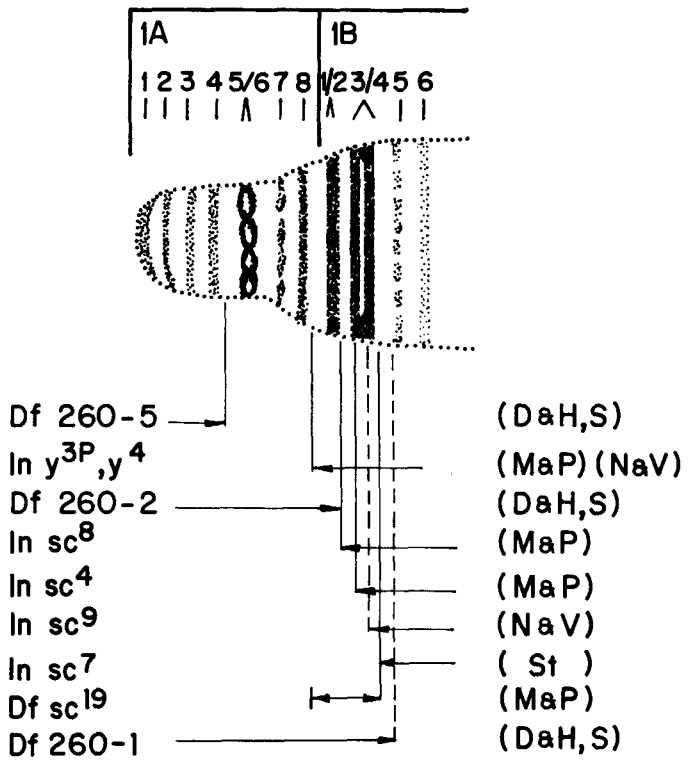

FIGURE 11.—Cytological breakpoints of rearrangements in the yellow achaete-scute region, in the map of BRIDGES (1938). Rearrangements as described in text. Vertical lines, location on the cytological map of the rearrangements (with uncertainties in dash lines). Data taken from: D + H: DEMEREC and HOOVER (1936), S. SUTTON (1943), M + P: MULLER and PROKOFYEVA (1935); N + V: NORTON and VALENCIA (1965), St: SCHULTZ, in LINDSLEY and GRELL (1968).

and *T(1;3)sc*^{l4}). Thus, it is conceivable that LR recombinants having left breakpoints in contact with heterochromatin and right ones in euchromatin would create a stronger variegation for the left genetic functions, *ac* and *sc*, and so lead to accumulative lethality, similar to that of *In(1)y*$^{+PL}$*sc*^{4R}. Under this interpretation, breakpoints assumed to be to the left and right of *l'sc* would now be all to the left of *l'sc*, but differ in their capacity to variegate for a gene located to the right of them in contiguity with heterochromatin. This interpretation, however, does not explain why the duplication elements of weak *sc* rearrangements like *sc*^{l9}, *sc*^{H}, or *sc*^{S2}, assumed now to be to the left of *l'sc*, should cover the lethal phenotype and largely the *sc* phenotype of *l'sc* chromosomes such as *In(1)sc*^{4L} *sc*^{9R}. Reciprocally, it is difficult to explain under this assumption why *Dp(1;Y)sc*^{S1} does not save *In(1)sc*^{4L}*sc*^{9R}, *Df(1)sc*^{H}, or even *Df(1)sc*^{l9}.

The lethality phase of *In(1)sc*^{4L}*sc*^{9R} and all deficiencies with breakpoints to the right of *l'sc* have a much earlier phenoeffective phase and a different chaeta phenotype than do deficiencies with breakpoints to the left of *l'sc* (GARCÍA-

BELLIDO and SANTAMARIA 1978). The existence of a distinct *l'sc* is supported by the fact that the lethality of *In(1)sc^{4L}sc^{9R}* cannot be rescued by the simultaneous addition of several different terminal duplications with breakpoints to the left of it, such as *Dp(1;Y)sc^{S1}* and *Dp(1;3)sc^{J4}*, or *Dp(1;Y)sc^{8}*. Thus, *l'sc*, although a synthetic lethal resulting from deficiencies, is a real entity.

The existence of euchromatic deficiencies phenotypically "lethal of scute" is further supported by the analysis of deficiencies resulting from the effects of a mutator mutant. M. M. GREEN supplied me with y^- chromosomes produced in a mutator stock originally y^2 in phenotype. I analyzed three of them expecting to see different phenotypes over the intercalary deficiencies or duplications of the scute region. All three of them were lethal over *Df(1)sc^{19}* and *Dp(1;2)sc^{19}*, but one of them was viable over *Dp(1;4)sc^{H}*, though lethal over *Df(1)sc^{8}*, *Dp(1;Y)sc^{S1}* and *Dp(1;Y)sc^{8}*. This genetic test suggests that this chromosome, $y^{-74i4.2}$, carries a deficiency that begins to the left of *Df(1)sc^{19}* and extends to the right of the breakpoint of *In(1)sc^{S1}* and even to the right of the lethal of scute, because the phenotype of *Dp(1;4)sc^{H}/y$^{-74i4.2}$* is a strong scute. The other two deficient y^- chromosomes, $y^{-74K10-1}$ and $y^{-74K10-3}$, are deficiencies extending even further to the right of *Dp(1;2)sc^{19}*. Cytologically, all three appear as terminal deficiencies with $y^{-74i4.2}$ having lost all bands to the left of *1B4* and the other two deficient through *1B5* or *6* (G. LEFEVRE, JR., personal communication).

Of the available point lethals in the tip of the first chromosome, none is allelic to the lethal of scute. A number of lethals in subdivisions *1A* and *1B* of the *X* chromosome were recovered by G. LEFEVRE, JR. and kindly sent to me. Eighteen of them, grouped in seven complementation groups, do not complement with *Df(1)260–1*. Yet all of these lethals complement with *Df(1)sc^{19}*, and none are saved by *Dp(1;2)sc^{19}*. In fact, between the right breakpoint of *Df(1)sc^{19}* and the right breakpoint of *Df(1)260–1*, two lethal complementation groups (six lethals) have been detected. All of these lethals showed complementation with the partial deficiencies *In(1)y^{+PL}sc^{8R}*, *In(1)sc^{8L}sc^{4R}* and *In(1)sc^{4L}sc^{9R}*. *Df(1)260–1/Dp(1;2)sc^{19}/Dp(1;Y)sc^{8}* and *Df(1)260–1/Dp sc^{H}* flies die in the pupal stages, and some were dissected out of the puparium. They do not show a more extreme *sc* phenotype than that of *sc^{19}* or *sc^{H}* hemizygous males. The lethals found proximal to *Df(1)sc^{19}* do not correspond to scute functions (GARCÍA-BELLIDO and SANTAMARIA 1978). Thus, the *l'sc* function seems not to be impaired by single point mutations; it can only be detected by deficiencies that remove or affect functions of both the left and right positions of the scute system.

DISCUSSION

Mutations at the achaete-scute system lead to patterns of chaeta suppression over the entire adult cuticle of Drosophila. The extent of this suppression depends on the particular allele. This quantitative effect has a qualitative expression in that the pattern of chaetae affected varies with the allele. This specificity of effect has led to the hypothesis that the achaete-scute system is a complex locus with qualitatively different functions (DUBININ 1929; SEREBROVSKY 1930).

It was early shown that the pattern of chaetae affected by a given allele could be modified by genetic (AGOL 1932; DUBININ 1933; STURTEVANT and SCHULTZ 1931) as well as environmental (GOLDSCHMIDT 1931; CHILD 1935a, 1936; IVES 1939) conditions. With the study of more alleles, a classification of alleles by their specific fields of action became more and more difficult. The pattern of suppression of a given allele would overlap that of another depending on whether it was studied in hemizygous males, in homozygous females, in *trans* heterozygotes with deficiencies or with another alleles. Some of these observations are confirmed and summarized in the present paper.

Subsequent genetic analysis and the possibility of visualizing in the salivary chromosomes the nature of the mutation permit a distinction between "point mutations" and chromosomal rearrangements. Surprisingly, the latter with one breakpoint in the achaete-scute region also show an allele-specific phenotype. This finding suggested the genetic divisibility of the achaete-scute function. The outstanding work of MULLER (MULLER 1935b; MULLER and PROKOFYEVA 1935; RAFFEL and MULLER 1940; see MULLER 1955) confirmed this assertion by analyzing the phenotype of left-right recombinants between inversions. They found that for a given pair of inversions (A and B) the phenotype of the left (A)–right (B) recombinant was different from that of the left (B)–right (A) recombinant and again different from that of either A or B. Since one of the LR combinations could be extreme in phenotype and the reciprocal combination nearly wild type, they concluded that the breakpoints of the inversions were genetically different, one combination creating a deficiency, and the reciprocal combination, a duplication. Thus, three breakpoints were operationally defined, delimiting at least three functions: achaete, scute and a lethal combination they called "lethal of scute". MULLER (1955) mentioned a total of 16 inversion breakpoints genetically analyzed by the LR test, and confirmed the same subdivisions. MULLER and PROKOFYEVA (1935) were able to assign some of these breakpoints to different bands in the salivary chromosomes, thus confirming cytologically the proposed subdivision of the achaete-scute system based on genetic behavior. In the present paper, we have repeated and confirmed some of these observations (Figure 6).

We have attempted a further analysis of the achaete-scute region using another genetic test. Making use of available or newly constructed duplications and deficiencies, we studied the phenotype of their combinations in males, trying to define "phenotypic breakpoints". The results are summarized in Figure 10.

As discussed above, (see Table 4 and Figures 7 to 9), we can create scute phenotypes, different from those of the rearrangements in heterozygotes, by combining duplications and deficiencies of their elements. This finding suggests that these rearrangements differ in their genetic breakpoints. Thus, we conclude that this region is subdivisible in that we can create genetic gaps between breakpoints, which are more extreme phenotypically, the more separated are the presumed breakpoints. Reciprocally, we can also create duplicated regions that always show the phenotype of the less extreme element of the combination. Based on the observed phenotypes, with rearrangements to the right of *l'sc*, we assume

that there should be a minimum of three different breakpoint positions (corresponding to *In(1)sc*^{9} and *In(1)sc*^{7}, to *T(1;2)sc*^{H} and *T(1;2)sc*^{82}, and to *T(1;2)sc*^{19}), and a maximum of five (Figure 10). It is important to recall that (1) the phenotype of the rearrangement elements in this region decreases in intensity from the neighborhood of *l'sc* [*In(1)sc*^{9}] distally to the right breakpoint of *T(1;2)sc*^{19} and (2) this order is also the order of recessiveness between rearrangements (Figure 10).

Similar considerations allow us to suggest a subdivision of the genetic region to the left breakpoint of *Df(1)sc*$^{10-1}$) and a maximum of eight [if only *In(1)sc*^{S1} between *l'sc* and *y* (corresponding to *In(1LR)sc*^{V1}, *In(1)sc*^{4}, *In(1)sc*^{S1} and *In(1)sc*^{L8}, to the right breakpoint of *Df(1)sc*$^{10-1}$, to *In(1)sc*^{8} and *T(1;3)sc*^{J4}, and to the left breakpoint of *Df(1)sc*$^{10-1}$) and a maximum of eight [if only *In(1)sc*^{S1} and *In(1)sc*^{L8} have identical breakpoints]. It should be remembered that, due to possible differential variegation of the deficiency and/or duplication element, the inferred breakpoints could be spuriously shifted or identified as being different. Again, as in the case of breakpoints to the right of *l'sc*, expressivity and recessivity decrease from the breakpoint of *In(1)sc*^{4}, the closest to *l'sc*, distally to yellow (Figure 10).

The inferred map of breakpoints based in the phenotype of rearrangements is supported by the few available cytogenetic data (compare Figures 10 and 11). Since the band terminology used by early authors is different from that of BRIDGES (1938), we have adapted all the available data to BRIDGES' map. The left breakpoints of *T(1;2)sc*^{19}, *In(1)y*^{sP} and *In(1)y*^{4} are between 1A8 and 1B1. The right breakpoint of *Df(1)260-1* is to the right of 1B4 (possibly at 1B5–6, G. LEFEVRE, JR., personal communication). Thus, the yellow achaete-scute functions are located in the interval of the two doublets 1B1–2 and 1B3–4. The breakpoints associated with achaete and the left scute region are at the left side of this interval; *In(1)sc*^{8} (and its genetic equivalent *Df(1)260-2*) have breakpoints between 1B2 and 3, that of *In(1)sc*^{4} is in 1B3–4. SCHULTZ reported *Df(1)sc*$^{10-1}$ to be deficient for 1B2 (see LINDSLEY and GRELL 1968). The breakpoints of the right scute region are to the right of that interval; *In(1)sc*^{7} as well as *T(1;2)sc*^{19} have breaks in 1B4–5, slightly to the right of, or at, 1B4. Thus, with the exception of *In(1)sc*^{9} (with reported breakpoint in 1B2–3), the cytogenetic data are in agreement with the genetic ones. It is remarkable that scute functions can be coded by lengths of DNA stretching over at least two large salivary chromosome bands.

Thus, the order of cytological breakpoints in the achaete-scute region is compatible with that of the phenotype, with the following characteristics. Rearrangements with breakpoints at either side of *l'sc* are scute in phenotype, but are more extreme the closer the breakpoint is to *l'sc*. The same conclusion is reached by the consideration of the scute phenotypes created by genetic gaps between duplications and deficiencies with breakpoints within the left or the right regions. The achaete-scute system appears as a tandem reverse repeat of similar functions at both sides of *l'sc*. Schematically, it can be described as follows:

$$. \; ac^{1}\text{–}ac^{2} \; . \; . \; . \; ac^{n}\text{–}sc^{\alpha 1}\text{–}sc^{\alpha 2} \; . \; . \; . \; sc^{\alpha n}\text{–}l'sc^{(n)}\text{–}sc^{\beta n} \; . \; . \; . \; sc^{\beta 2}\text{–}sc^{\beta 1} \; .$$

The number of functions so defined depends on the power of resolution we used to distinguish phenotypes. It is important, however, to notice that there are no qualitative differences between the phenotypes of rearrangements with breakpoints to the left or to the right of *l'sc*, nor of the synthetic deficiencies created within the left (sc^{α}) or the right (sc^{β}) groups. In all the rearrangements studied, the scute phenotype affects the same seriation of chaeta sites, although to different extents (Figures 7 to 9). Thus, the scute functions affected by rearrangements appear, based on their phenotypes, to be redundant. *Trans* heterozygotes of the different rearrangements, within the *ac*, the sc^{α} or the sc^{β} groups, as well as between them, show an achaete-scute phenotype (Table 4, Figures 7 to 9). It is interesting to recall that the LR inversion combinations that create a duplication (*i.e.*, $sc^{4L}sc^{8R}$) are phenotypically wild type (Table 2), and the heterozygous deficiencies over a normal chromosome are also wild type. Thus, we interpret these findings as indicating that those functions are not redundant, but rather reiterative, meaning that the wild-type phenotype requires the function of all of them. We assume that combinations of different functions are required for the normal differentiation of a given chaeta or, alternatively, that all the chaetae require different amounts of all the functions of the system.

The noncomplementation of the *trans* heterozygotes could be interpreted as resulting from a *cis*-polar effect of the rearrangements. However, even if the *trans* heterozygote involves rearrangements with breakpoints to the left and to the right of *l'sc*, the phenotype is like that of the weaker rearrangement. Moreover, there is always complete complementation with respect to *l'sc*. Thus, if a polar effect exists, the direction of the polarity is always distalward from *l'sc*. The nature of the polar effect cannot be explained in terms of inactivation of functions distal to the site of the breakpoint, for duplication elements are capable of rescuing the phenotype of the deficiencies if they overlap. That is, the functions carried by the duplication element can be expressed also. Thus, the different functions probably have their own initiation sequences for control of transcription.

We do not know to which of these postulated functions the point mutants correspond. On the basis of their phenotype and behavior in complementation tests, they may be subdivided into an achaete and a scute group. However, any attempt to assign the mutants of the latter group to either the sc^{α} or sc^{β} groups must wait until a meiotic recombinational analysis is carried out. They fail to complement, and they show a similar phenotype with all of the intercalary deficiencies tested. Complementation analysis among them gives similar results to that of rearrangements; scute point mutants fail to complement each other although to different degrees, and in general heterozygotes show the phenotype of the weakest allele in the combination. It is possible that they correspond to the inactivation of individual functions, although a possible *cis*-polar effect among them cannot be discarded altogether. Especially striking is the behavior of sc^{3-1} (and to some extent sc^{2}), which is phenotypically wild type in hemizygous or homozygous condition, but extreme scute and even lethal over deficiencies. The same uncertainty applies to the localization of the wild-type function of the *Hw* phenotype. *Hw* is a mutation that maps in the achaete-scute region. However, its

phenotype does not correspond to that of the deficiency (DEMEREC and HOOVER 1939). The interpretation of those authors that *Hw* corresponds to a duplication of some achaete-scute function is reinforced by the observation that LR recombinants such as *In(1)sc^{4L}y^{sPR}* and *In(1)sc^{4L}sc^{8R}* (Table 2) show an extreme *Hw* phenotype. It is interesting that this phenotype does not appear in males with duplications of the chromosome tip such as *Dp(1;2)sc^{82}*, *Dp(1;2)sc^{19}*, or even longer duplications. Thus, the *Hw* effect seems to be associated with *cis* rearrangements (duplications) within the achaete-scute region. *Hw* phenotype may result also from variegation of the proximal heterochromatin of the *X* chromosome upon the *sc$^{\alpha}$* region, as in *In(1)sc^{8}* and *In(1)sc^{4}* (RAFFEL and MULLER 1940).

The above interpretation of the organization of the achaete-scute system leads to a number of questions. Why does the order of rearrangements from more to less extreme correspond to the order of the inferred breakpoints? Why is this order symmetric with respect to *l'sc*? What are the functional relationships of *l'sc*, *sc$^{\alpha}$* and *sc$^{\beta}$*? As to the first two questions, it can be argued that the achaete-scute system originated as a tandem reverse duplication of the same genetic material and that became insufficient in a single dose later in evolution. The decreasing order of strength of the scute phenotypes at both sides of the *l'sc* site reflects some functional organization of the scute system. Among many alternatives, it is plausible that some kind of *cis* control is exerted by the *l'sc* site upon neighboring sites.

The existence of a *l'sc* locus, inferred by the phenotype of LR inversion recombinants, was confirmed by the behavior of duplication-deficiency combinations. Cytological data corroborate the existence of distinct breakpoints to the left and to the right of it. However, the fact that we do not know of any *l'sc* point mutation among several lethals recovered from this chromosome region leads to the conclusion that it is a synthetic lethal resulting from a genetic deficiency. The finding that the lethality of *l'sc* in *In(1)sc^{4L}sc^{9R}* cannot be rescued by the simultaneous addition of several duplications with breakpoints distal to *In(1)sc^{4}* suggests that its function is different from that of the remaining achaete-scute region. A developmental analysis of this lethal combination has shown that its phenotype is related to that of the achaete-scute system (GARCÍA-BELLIDO and SANTAMARIA 1978). Whereas deficiencies for *l'sc* probably cause insufficiencies in the normal differentiation of the central nervous system, deficiencies for achaete-scute cause an homologous insufficiency in the differentiation of the peripheral nervous system with the total absence of innervated chaetae. Whereas the former are early embryonic lethals, the latter are viable until metamorphosis and may even emerge as adults. If the "lethal of scute", like scute, is also complex, it would be understandable why no point mutants have been so far detected. It is expected that only deficiencies will have a striking behavioral or lethal phenotype.

SUTTON (1943) found that a variety of X-ray-induced rearrangements with breakpoints in different positions in the tip of the *X* chromosome may or may not have scute phenotypes. She discussed the possibility that scute phenotypes are due to position effects upon a single locus that codes for the scute function. Under this assumption, the point-mutant alleles would correspond to mutations

in this locus; the scute rearrangements may correspond to interference with this locus. If scute phenotypes result from position effects upon a single function, it is difficult to explain their pattern specificity. Even more difficult to explain is why duplication-deficiency combinations with elements of these rearrangements cause phenotypes more extreme than that of the most extreme rearrangement of the combination. SUTTON (1943) further reported that scute phenotypes are caused by rearrangements with breakpoints between 1A8 and 1B5, the same regions studied here. The present results could be accommodated in a model that suggests that all the functions of this system represent reiterative, but not identical, signals that combine in different ways for control of differentiation. From a formal point of view the functional product of the achaete-scute system can be visualized as a multimeric complex made up of individual monomeres, each coded by an independent length of DNA of the achaete-scute locus. That model does not explain in itself the lack of complementation between different alleles (point mutants as well as rearrangements). It is further complicated by the assumption that transcription and/or translation and assembly of the multimeric complex preferentially occurs upon sequences coded by each homolog. This in turn leads to the puzzling conclusion that *cis*-coordinated transcription and/or translation extends over several chromomeres involving many thousands of nucleotides.

It is interesting to recall the existence in Drosophila of other genetic systems having striking organizational similarities. LEWIS (1964) has suggested that the bithorax pseudoallelic system is cytologically a tandem repeat of two bands or doublets, which possess related functions that can be separated by rearrangements. It has a *cis*-control region in its middle and shows polar effects between point mutations at both sides of it. In both systems, bithorax and achaete-scute, related functions are stretched over many thousands of nucleotides with *cis*-relationships, with no known parallel to the organization of the prokaryotic chromosome. The genetic organization of the Abruptex-Notch system (WELSHONS 1965; FOSTER 1975; PORTIN 1975) also shows similarities with the achaete-scute system, such as the existence of tandem repeated related functions and complex *trans* effects in heterozygotes. Genetic similarities can also be found between scute and the rudimentary locus. In this complex locus, mutants affecting different enzymes of the pyrimidine biosynthetic pathway have a similar phenotype, possibly due to the fact that these enzymes are functionally arranged in a multienzyme complex (see RAWLES and FRISTROM 1975).

The shortcomings of analysis like the present one is that the observed phenotypes are far separated from the primary gene product. Thus, any proposal as to the genetic organization of these loci and their regulatory functions are necessarily speculative. However, the possibility that these systems may represent models of genetic organization characteristic of eukaryotic organisms makes them interesting.

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