THE REGIONAL EFFECTS OF TWO MUTANTS IN *DROSOPHILA* ANALYZED BY MEANS OF MOSAICS

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THE nature of the effect of genes that control the regional pattern of differentiation of cells during ontogeny is a fundamental problem in developmental genetics. In the present investigation, two mutations which have rather extensive regional effects on bristle development in *Drosophila* are subjected to the genetic mosaic technique permitting a decision as to whether or not they affect bristle pattern formation.

The dorsal part of the thorax of *Drosophila melanogaster*, the mesonotum, is derived from the two dorsal mesothoracic discs of the larvae. During pupation, the cells from the left and right discs take their place on the future mesonotum meeting at the dorsal midline. The mesonotum is covered by large and small bristles, known respectively as macrochaetae and microchaetae, whose formation has been shown to be under genetic control. In addition, there is genetic control of their position on the thorax. The investigation of the mechanisms involved in setting aside the presumptive bristle-forming cells in their specific locations is aided by the fact that many mutant genes are known which alter the typical number and arrangement of chaetae.

The absence of one of the bristles making up the normal complement of chaetae may be the result of either of two phenomena. A mutant gene may alter the normal processes which determine the specific sites of chaetae formation in the presumptive mesonotal tissue in such a way that one or more of the sites are missing. On the other hand, the action of the mutant gene may not alter the "site determining prepatter" but may affect the cells in particular regions of the presumptive mesonotum in their reaction to previously occurring bristle determining events. Similar alternatives can be applied to mutations which add to rather than subtract from the normal number of bristles.

In 1954 STERN proposed that these possibilities to explain the effects of mutations on mesonotal chaetae could be distinguished from each other by the investigation of genetic mosaics. He found that the recessive gene *achaete* (*ac*-1,0.0+), which removes the posterior and frequently the anterior dorsocentral bristles from the mesonotum, behaves autonomously in mosaics in which *ac* cells occur on a phenotypically normal +/*ac* background, suggesting that the mutant allele

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renders cells either incapable of responding to an initial prepatter or unable to complete differentiation. In an achaete background, $+ac$ cells also gave results consistent with autonomous behavior. Though most of the epidermis was ac , posterior dorsocentral bristles were found when $+ac$ cells were present at the posterior dorsocentral site. This is again confirmation of the fact that the mutant allele ac affects the cellular response to the bristle prepatter or the ability to complete differentiation, and not the prepatter itself.

Using the mosaic technique, several other genes which affect thoracic bristle development have been studied. All those tested, including scute (STERN and SWANSON 1957; YOUNG and LEWONTIN 1966), Hairy-wing (GOTTLIEB 1964), Theta (STERN 1956) and hairy (STERN 1954), act in a way similar to achaete (STERN 1954; ROBERTS 1961). An example of a probable prepatter mutation, one affecting the leg, has recently been reported (STERN and TOKUNAGA 1967).

The present investigation is an extension of the search for genes which control thoracic bristle pattern in *Drosophila*. For this purpose, two mutants which had rather extensive regional effects on the bristles in contrast to those affecting only a few limited sites were analyzed using the mosaic technique. One of them, Tufted, results in the appearance of numerous extra macrochaetae on the thorax. The other, $l(1)N^B$, in certain genotypes results in the absence of almost all of the microchaetae and many macrochaetae. The extreme nature of these genes, suggested that perhaps they were involved in the formation of the bristle prepatter rather than in the control of the cellular response to the prepatter.

The Investigation of Tufted

The dominant gene Tufted (*Tft*) is located on the left arm of the second chromosome. RITTERHOFF (1952) located Tufted between the genes black (48.5) and purple (54.5). Recent data of TOKUNAGA (1967) place *Tft* to the left of Bristle (54.8) with a recombination frequency of 1.2%. The Tufted phenotype is characterized by numerous extra macrochaetae in the postalar, dorsocentral and scutellar regions (Figure 1A). Tufted derives its name from the distribution of bristles on the posterior mesothorax. The density of chaetae in the scutellar region of heterozygotes and especially homozygotes is often so great as to give the appearance of tufts of bristles. In addition to the bristle abnormalities, the posterior part of the mesonotum in Tufted flies appears wider than normal. In homozygous and heterozygous females, the scutellum is greatly reduced and the scutoscuteellar suture is almost absent. In heterozygous males, the scutellum is more often nearly normal (Figure 1B). The penetrance of Tufted in both males and females is 100%.

The effects of Tufted on bristle development were analyzed by means of mosaics in which wild type (non-Tufted) cell patches were present in the posterior region of the mesonotum composed mainly of tissue heterozygous for Tufted. Such mosaics occur as a consequence of somatic crossing over in $Tft/+$ individuals.

FIGURE 1.—The posterior portion of the mesonotum of a female (A) and male (B) heterozygous for *Tft*.

MATERIALS AND METHODS

In order to provide a marker to detect cell segregants resulting from somatic crossing over, a normal allele of the gene yellow ($1,0,0$) was introduced distal to Tufted at a position close to the gene dumpy ($2,13,0$). This was made possible by using the *sc*¹⁹ translocation (see TOKUNAGA and ARNHEIM 1966). Figure 2A shows the second chromosome genotype of the individuals which

FIGURE 2.—(A) The zygotic second chromosome genotype of larvae irradiated in the Tufted experiment. The open circle represents the centromere while (y) symbolizes the absence of the y^+ insertion. Possible complementary cell segregants after somatic crossing over in region 1 (B), in region 2 (C), and in regions 1 and 2 (D) are shown.

were irradiated and examined for mosaic patches. The X chromosomes in both males and females have genotypes leading to a yellow phenotype (males are hemizygous for the *sc¹⁹* deficiency for γ ; females are heterozygous for γ and the *sc¹⁹* deficiency). Thus, were it not for the presence of the γ^+ gene on one of the second chromosomes, these individuals would show yellow bristle and body coloration.

Somatic crossing over in chromosome region 1 between *Tft* and the centromere (Figure 2B) can result in γ^+Tft/γ^+Tft and $(\gamma)Tft/(\gamma)Tft$ cell patches. The symbol (γ) indicates the absence of the γ^+ insertion. Somatic crossing over in chromosome region 2 between the γ^+ insertion and *Tft* (Figure 2C) can result in $(\gamma)Tft/(\gamma)Tft$ and γ^+Tft/γ^+Tft tissue patches.

If the normal allele of *Tft* behaves autonomously in mosaics, cell patches with the yellow non-Tufted genotype, $(\gamma)Tft/(\gamma)Tft$, resulting from somatic crossing over in region 1, would have a yellow non-Tufted phenotype while patches with the yellow Tufted genotype, $(\gamma)Tft/(\gamma)Tft$, resulting from somatic crossing over in region 2, would have a yellow Tufted phenotype. If *Tft* behaves nonautonomously, cells having the yellow non-Tufted or the yellow Tufted genotype will have a yellow Tufted phenotype. Thus if the yellow patches are all Tufted in phenotype it would indicate that *Tft* behaves nonautonomously. The appearance of both Tufted and non-Tufted yellow patches would signify autonomous behavior of *Tft*.

Mosaic production: Larvae of the genotypes $\gamma^+Tft/(\gamma)Tft$ were irradiated on Petri dishes containing standard *Drosophila* medium 24 to 48 hours after hatching. This leads to an increase, over that occurring spontaneously, in the frequency of somatic crossing over (BECKER 1957). A dose of 1500r at the rate of 75r/min was delivered for a total time of 20 minutes (150kv, 4ma, 1.5 mm aluminum inherent filtration plus 0.75 mm aluminum external filtration). After emergence, the flies were inspected for mosaic patches with 32 $\times$ magnification. All experiments were conducted at $25 \pm 1^\circ\text{C}$.

RESULTS

Nineteen individuals out of a total of 3370 males and females of the $\gamma^+Tft/(\gamma)Tft$ genotype that were recovered after irradiation had yellow patches in the posterior mesothorax region resulting from somatic crossing over. After the conclusion of this experiment TOKUNAGA and ARNHEIM (1966) produced 72 additional specimens with yellow patches. In regard to the Tufted phenotype, this combined total of 91 spots fell into two strikingly different classes. In 51 cases the patches were clearly non-Tufted (for examples see Figures 3 and 4A-D)

FIGURE 3.—A $\gamma^+Tft/(\gamma)Tft$ individual with a yellow non-Tufted mosaic patch on the right side of the mesonotum. Figure 4B indicates the extent of the $(\gamma)Tft/(\gamma)Tft$ tissue. (In Figure 4B the patch is shown as if it had occurred on the left side of the mesonotum.)

FIGURE 4.—Dorsal view of half-mesothoraxes. The open circles represent the positions of macrochaetae. All the mosaic patches are shown as if they had occurred on the left half of the mesonotum. A-D, $\gamma^+Tft/(\gamma)Tft^+$ half-thoraxes with non-Tufted mosaic patches. The stippled area has yellow bristles and is non-Tufted in phenotype. E-H, $\gamma^+Tft/(\gamma)Tft^+$ half-thoraxes with Tufted mosaic patches. The stippled area has yellow bristles and is Tufted in phenotype. I, a half-thorax with crosshatching in the area used for microchaetae counts (thoracic area). J-L, mosaic fa^{no}/l half thoraxes with fa^{no}/fa^{no} tissue (stippling) in the thoracic area.

and in 40 cases they were equally clearly Tufted (for examples see Figures 4E-H). These latter yellow Tufted patches are evidence for crossing over to the left of *Tft* (region 2) whereas the yellow non-Tufted patches resulted from crossing over to the right of *Tft* (region 1) and autonomous expression of the genotypically non-Tufted cells.

The possibility was considered that the phenotypically yellow Tufted patches actually were genotypically non-Tufted like the phenotypically non-Tufted patches but that the non-Tufted genotype varied in its expression in mosaics sometimes acting autonomously and at other times nonautonomously. This is very unlikely since there were no intermediate grades of expression of the yellow patches. The distinction between the Tufted and non-Tufted phenotypes was always made without difficulty. In addition, if patches homozygous for *Tft*⁺ sometimes exhibited a *Tft* phenotype, a positive correlation between the time during ontogeny when the loss of *Tft* occurs by crossing over and the degree of tuftedness of the *Tft*⁺/*Tft*⁺ tissue might be expected. The evidence of TOKUNAGA and ARNHEIM (1966), however, is not consistent with this expectation since late crossing-over events produce a greater proportion of phenotypically non-Tufted patches than early crossing-over events. Support for the idea that the yellow Tufted tissue areas result from crossing over between γ^+ and *Tft* also comes from the observation of three mosaic flies which had non-Tufted portions of the posterior mesothorax but with black bristles. The most likely explanation for these individuals is based upon the occurrence of double crossing-over events. As seen in Figure 2D, crossovers in regions 1 and 2 can give rise to cells which lack *Tft* but still retain γ^+ . These cells, under the assumption of autonomy of differentiation of wild-type tissue, would be expected to form only the normal bristles but

black in color. Finally, analysis of the topological distribution of the mosaic patches indicates that every region of the posterior mesonotum is capable of expressing autonomy for Tufted. Thus it cannot be argued that all the yellow patches resulted from crossing over in region 1, but that in certain mesonotal regions these non-*Tft* cells formed patches having the Tufted phenotype.

We may conclude, therefore, that wild-type cells which are produced by somatic crossing over are not influenced in their development of macrochaetae by surrounding tissues containing the Tufted gene. Cells of the *Tft* genotype have an altered response to the normal bristle prepatter in the posterior mesothoracic region.

The Investigation of $l(1)N^B$

The allele $l(1)N^B$ (hereafter symbolized by *l*) is a point mutation at the Notch locus (1,3.0) (WELSHONS 1965). Flies heterozygous for *l* and a wild-type allele have fewer mesonotal bristles than normal individuals. The dominant effect of *l* in regard to bristle formation makes it possible to assess its developmental action in a manner similar to that employed for Tufted. The heterozygous combination of *l* and wild type (*l/+*) was thought to be unsuitable for an analysis of genetic mosaics since too few bristles were expected to be present in these flies. The combination of *l* and its pseudoallele facet-notchoid (fa^{no}) was, however, found to be appropriate for such a study. For this investigation only one small portion of the mesonotum was chosen for detailed analysis. This region, selected for its convenient boundaries and designated in this paper as the thoracic area

FIGURE 5.—The total number of microchaetae ($fa^{no}/l + fa^{no}/fa^{no}$) (curve A) and fa^{no}/l microchaetae (curve B) in the thoracic areas of flies with fa^{no}/fa^{no} tissue patches in the thoracic area plotted against the size of the fa^{no}/fa^{no} tissue patch.

FIGURE 6.—(A) The mesonotum of a fa^{no}/fa^{no} individual. The thoracic area is stippled. (B) The mesonotum of a $l/l;Dp$ individual. The thoracic area is stippled.

(see Figure 4I), has on the average approximately 11 microchaetae in flies of the fa^{no}/l genotype whereas fa^{no}/fa^{no} flies have approximately 26 such bristles as is typical of wild-type individuals (Figure 6A). Thus, to determine whether l acts to alter the response of potential bristle forming cells in the thoracic area to the normal prepattern or actually affects the prepattern itself, homozygous cell patches were produced by somatic crossing over in mesonotal tissue heterozygous for l . Such crossing over in fa^{no}/l flies can result in both fa^{no}/fa^{no} and l/l cell segregants. If the l mutant inhibits bristle formation in fa^{no}/l individuals by altering the basic pattern of organization of the mesothoracic discs, then fa^{no}/fa^{no} cells in a thoracic area composed mainly of fa^{no}/l tissue should produce bristles as frequently as the fa^{no}/l cells. If, on the other hand, the l mutant inhibits bristle formation by altering the response of the fa^{no}/l cells to the normal bristle prepattern then fa^{no}/fa^{no} cells in a disc composed of fa^{no}/l tissue should respond to the wild-type prepattern by producing numbers of microchaetae normal for thoracic areas of fa^{no}/fa^{no} individuals.

These expectations for the behavior of mosaic spots are contingent upon an analysis of small mosaic patches. A dorsal mesothoracic disc composed almost entirely of fa^{no}/fa^{no} tissue would be expected to behave autonomously except if there is some interaction between the left and right discs. Previous work has at best given only the slightest indication of interactions between discs (see KING 1964; PANTELOURIS and WADDINGTON 1955; MURPHY 1967).

MATERIALS AND METHODS

In order to detect fa^{no}/fa^{no} cell patches resulting from somatic crossing over, a stock was obtained containing both fa^{no} and singed-3 ($sn^3-1,23.0$). The sn^3 phenotype, serving as a marker in mosaics, is characterized by crooked bristles. The l bearing chromosome carries the yellow mutant ($\gamma-1,0.0$) as a marker gene. The genotype of the irradiated flies was therefore $fa^{no}sn^3/\gamma l$.

For reasons to be discussed more fully in a later section the duplication $Dp(1;2R)W^{s1b7}$ (hereafter symbolized by Dp) was introduced into the stock of flies to be irradiated. This dupli-

cation is carried on the right arm of the second chromosome and covers both the Notch and white loci (LEFEVRE 1952). *Dp* was segregating, therefore, among the irradiated flies. Although *fa^{no}/l* and *fa^{no}/l;Dp* flies differ with respect to the average number of microchaetae on the thoracic area, approximately 10 and 12 respectively, the difference is insignificant with respect to the present study since the decision as to whether *fa^{no}/fa^{no}* cells are behaving autonomously or non-autonomously will depend upon whether *fa^{no}/fa^{no}* tissue patches form microchaetae at the frequency seen in whole *fa^{no}/fa^{no}* individuals (approximately 26 microchaetae per thoracic area) or at a frequency roughly 50% of this as is typical of *fa^{no}/l* flies (with or without *Dp*). In the discussion on the behavior of *fa^{no}/fa^{no}* cell patches, therefore, no distinction will be made between flies with and without *Dp*.

Larvae of the genotype *fa^{no}sn³/yl* were irradiated under the same conditions as described in the Tufted experiment. After eclosion the flies were fixed in alcohol and subsequently inspected under a dissecting microscope at a magnification of at least 36 $\times$. If present in the thoracic area the number of normal (*fa^{no}/l*) microchaetae, and singed-3 (*fa^{no}/fa^{no}*) and yellow (*l/l*) microchaetae resulting from somatic crossing over were recorded. All experiments were performed at $25 \pm 1^\circ\text{C}$. The discussion of cells homozygous for *l* will be in a later section.

RESULTS

A total of 1242 *fa^{no}/l* flies were inspected for mosaic spots. Among them 74 were found with a *fa^{no}/fa^{no}* tissue patch in the thoracic area (one or more *sn³* bristles). Drawings showing the areas of the thorax covered by mosaic patches are shown for three of the 74 cases in Figures 4 J-L. Figure 5 curve A shows that the average number of bristles on the thoracic area increases in proportion to the size of the *fa^{no}/fa^{no}* tissue patch in that area. Figure 5 curve B shows that the observed increase in bristle number in thoracic areas with *fa^{no}/fa^{no}* tissue must be due entirely to bristle formation by the *fa^{no}/fa^{no}* cells and not to bristle formation by *fa^{no}/l* cells under the influence of *fa^{no}/fa^{no}* tissue since the number of *fa^{no}/l* bristles in the thoracic area decreases as the size of the *fa^{no}/fa^{no}* tissue patch in the area increases. These data indicate that the *fa^{no}/fa^{no}* cells act autonomously in bristle differentiation.

Instead of interpreting the observation that thoracic areas with *fa^{no}/fa^{no}* tissue have more bristles than areas composed entirely of *fa^{no}/l* cells in terms of autonomy, an alternative explanation could be considered according to which the flies with mosaic patches happen to have a residual genotype leading to high microchaetae numbers. Since every individual possesses two thoracic areas, a test of this hypothesis can be made by comparing the total number of bristles in the area on the side with the mosaic patch to the number on the opposite, non-mosaic side. Table 1 shows that the number of bristles in the mosaic patch on one side of the fly is not correlated with the total number of bristles present in the thoracic area of the other side and that there are in each size class (with one exception) more bristles on the mosaic than on the opposite side. It would appear, therefore, that the correlation between the total bristle number of a thoracic area and the size of the *fa^{no}/fa^{no}* tissue patch on that same area is actually the result of the greater ability of wild-type tissue (*fa^{no}/fa^{no}* cells are normal with respect to bristle formation) to initiate and complete bristle differentiation than of *fa^{no}/l* cells.

Additional evidence that the *l* mutation alters the competence of epidermal

TABLE 1

Size distribution of fa^{no}/fa^{no} mosaic spots

Size of mosaic spot (number of sn^3 bristles)	Average number of bristles per thoracic area, $\pm$ se		Number of individuals
	Mosaic side	Other side	
1-4	12.5 ± 1.0	12.6 ± 0.6	25
5-8	12.9 ± 0.8	11.7 ± 1.0	17
9-12	16.8 ± 0.9	12.6 ± 1.2	12
13-16	18.0 ± 1.0	11.3 ± 1.8	6
17-20	20.8 ± 1.9	11.4 ± 1.4	5
21-24	23.4 ± 0.5	11.6 ± 1.0	9

cells in the thoracic area and not the prepatter itself comes from the analysis of l/l cell segregants resulting from somatic crossing over in fa^{no}/l individuals. Both l/l ; Dp and l/l cells were found to be viable in mosaics. If cells homozygous for l behave autonomously with respect to bristle differentiation in fa^{no}/l mosaics almost no yellow microchaetae would be expected to be found on the thoracic area. This expectation is based on the fact that l/l ; Dp individuals have an average of less than one (0.03) microchaeta per thoracic area (Figure 6B). On the 1242 fa^{no}/l individuals examined 39 yellow bristles (17 l/l and 22 l/l ; Dp) were observed on the thoracic area whereas 691 sn^3 bristles representing the complementary fa^{no}/fa^{no} cell segregants were found. Assuming that the frequency of l/l and fa^{no}/fa^{no} patches produced by somatic crossing over are equal (see however GOTTLIEB) the observed deficiency of l/l bristles is consistent with the interpretation that cells carrying l behave autonomously and have an altered response to the normal prepatter.

DISCUSSION

This investigation adds two more cases to the list of thoracic bristle mutants analyzed by the mosaic technique for their influence on the determination of bristle pattern. All those tested, including ac (STERN 1954; ROBERTS 1961), Hw (GOTTLIEB 1964), Θ (STERN 1956), h (STERN 1954), sc (STERN and SWANSON 1957; YOUNG and LEWONTIN 1966), $l(1)N^B$ and Tufted, have been found to alter the competence of cells in specific regions of the mesonotum to initiate and/or complete bristle differentiation. Mutations which result in the homeotic transformation of the antenna (ROBERTS 1964), leg (TOKUNAGA and STERN 1965) and mesothorax (LEWIS 1963) have also been investigated by the mosaic technique. Without exception these mutations have also been found to affect cell competence.

One genotype, ey^D , is thought to alter a prepatter involved in leg morphogenesis (STERN and TOKUNAGA 1967). The preponderance of mutations affecting cell competence could be accounted for if the processes of pattern formation were intimately related to vital functions and mutations affecting these events were for the most part lethal (URSPRUNG 1963; VON BORSTEL 1963). Thus, for instance, the arrangement of cells within a tissue mass might influence the setting aside of

strategically located cells for particular developmental pathways. If this were true, mutants changing the prepatter might be those which affected the basic cellular organization of the imaginal discs. This in turn might involve abnormal cell movements and hence interfere with basic morphogenetic processes necessary for successful development.

To explain away the rare discovery of prepatter mutations by suggesting that they are for the most part lethal is not entirely satisfactory. The mosaic technique, however, allows the relatively rapid analysis of mutations suspected of playing a role in pattern determination and further studies will undoubtedly lead to a better understanding of the viability and mode of action of prepatter mutations.

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SUMMARY

The genes Tufted and $l(1)N^B$ have rather extensive regional effects on the differentiation of the mesonotal bristles in *Drosophila melanogaster*. The former adds macrochaetae to the posterior mesonotal region while the latter removes numerous microchaetae from the mesothorax. An analysis of genetic mosaics has shown that both of these mutations affect the competence of cells in specific regions of the mesonotum to initiate and/or complete bristle differentiation. The extreme phenotype manifested by individuals carrying these mutations therefore is not the result of a change in the underlying prepatter.

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