REVERTANTS OF DOMINANT MUTATIONS ASSOCIATED WITH THE ANTENNAPEDIA GENE COMPLEX OF *DROSOPHILA MELANOGASTER:* CYTOLOGY AND GENETICS

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ABSTRACT

Using X-ray mutagenesis we have induced and recovered phenotypic revertants of four dominant mutations thought to be associated with the Antennapedia complex of *Drosophila melanogaster.* These include seven revertants of Antennapedia-73b ($Antp^{73b}$), six of Extra Sex Combs of Wakimoto (Scx^{W}), three of Deformed (*Dfd*) and one of Humeral (*Hu*). Fifteen of the 17 revertants are associated with chromosomal aberrations and localize $Antp^{73b}$, Scx^{W} and *Hu* to polytene chromosome bands 84B1,2. The *Dfd* lesion is apparently located in or adjacent to bands 84A4,5. Since all of the dominants are reverted by events that delete their respective chromosomal loci, we conclude that all four are the result of a gain-of-function lesions. Complementation analysis of the various revertant chromosomes has shown that Scx^{W} and *Hu* are dominant allelic variants of the *Antp* locus. The *Dfd* lesion represents a dominant mutation at a locus just proximal to *Antp* and previously only occupied by recessive lethal mutations. Characterization of the revertants of Scx^{W} and a comparison with the properties of the original mutation has revealed that the original lesion has effects on both the *Antp* and Sex Combs Reduced (*Scr*) loci and that these defects are in some cases separable by the reverting event.

THE Antennapedia gene complex (ANT-C) of *Drosophila melanogaster* is a set of closely linked genes that function in early developmental decisions leading to the correct identity of head and thoracic segments (KAUFMAN 1978; KAUFMAN, LEWIS and WAKIMOTO 1980; LEWIS *et al.* 1980a,b; WAKIMOTO and KAUFMAN 1981; DENELL *et al.* 1981; STRUHL 1981). At the time that this work was initiated, reversion experiments with $Antp^{Ns}$ (Nasobemia, an allele of *Antp*) and *Msc* (Multiple Sex Combs) had indicated that at least part of this gene complex was associated with polytene bands 84B1,2 (DENELL 1972a,b, 1973; DUNCAN and KAUFMAN 1975). The rest of the ANT-C was operationally defined as all lethal and visible mutations exposed by *Df(3R)Scr* (84A2-84B1) that had demonstrable effects on the development of the anterior portions of the embryo (WAKIMOTO and KAUFMAN 1981).

A productive method for genetically and cytologically characterizing a particular region of a chromosome is to study X-ray-induced revertants of a dominant mutation which is resident in the area of interest. By revertant, what is

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meant here is the loss of an aberrant phenotype associated with a dominant mutation, not a state of reversion on the molecular level leading to a normal DNA sequence. This approach has yielded information about the cytological locations and genetic natures of several dominant mutations (SUTTON 1943; DENELL 1972a,b; LIFSCHYTZ and FALK 1969a,b; MANGE and SANDLER 1973; DUNCAN and KAUFMAN 1975; STRUHL 1981). The determination of the cytological location of a mutation can be ascertained if it is assumed that chromosome breakpoints induced by these reversion events lead to a loss or alteration of the mutant gene's function. Thus, a common breakpoint shared by a set of revertants should reveal the cytological location of the original mutation. Moreover, that a dominant mutation may be reverted by inducing deletions of its locus indicates that the original mutation resulted from a gain of function (LINDSLEY *et al.* 1972).

The experiments reported here studied the induction and cytogenetic and phenotypic characteristics of revertants of four dominant mutations which evidence suggests are associated with the ANT-C. These mutations are Scx^{W} (Extra Sex Combs of Wakimoto), *Hu* (Humeral), *Dfd* (Deformed) and $Antp^{73b}$ (an allele of Antennapedia). The EMS-induced Scx^{W} (this mutation was designated as *EfW15* in previous reports from this laboratory) mutation was defined as an allele of *Antp* on the basis of its failure to complement the recessive lethality associated with the *Antp* locus and because it causes a homoeotic transformation of the embryonic ventral mesothorax and metathorax to prothorax (LEWIS *et al.* 1980a; WAKIMOTO and KAUFMAN 1981). The Scx^{W} mutation exhibits further interactions with the *Scr* (Sex Combs Reduced) locus which will be discussed in the body of this paper. $Antp^{73b}$ (a spontaneous mutation recovered by M. GREEN) fails to complement the recessive lethality of a majority of lethal *Antp* alleles and was previously reported as being cytologically aberrant in the 84B-C polytene region (KAUFMAN, LEWIS and WAKIMOTO 1980; LEWIS *et al.* 1980a). These authors also suggested that *Hu* and *Dfd* were mutations in the ANT-C or its chromosomal environs. The *Hu* mutation is associated with a double inversion with one breakpoint at 84B1,2. Adult flies carrying *Hu* have extra bristles on the humeral callus and fine bristles on the propleura. In heterozygous condition with deficiencies that delete 84B1,2, or with a majority of EMS-induced recessive *Antp* alleles, the phenotype of *Hu* is enhanced relative to *Hu*/+ and is similar to that of *Hu/Hu*. The *Dfd* mutation can also be mapped to 84A-B, the site of the ANT-C, in that heterozygotes for *Dfd* and a deficiency for the ANT-C have reduced viability. The *Dfd* phenotype involves a reduction in eye facets, disruption of orbital bristles and vibrissae and loss or duplication of the maxillary palps (SINCLAIR 1977). In addition, SINCLAIR had localized *Dfd* to this region on the basis of recombinational mapping.

The purpose of this work was first to determine whether these four mutations mapped cytologically to the polytene chromosome region in which the ANT-C resides. Second, by our ability or inability to revert these mutations, we wished to determine whether the mutant phenotypes resulted from a gain or a loss of function. Third, by inducing overlapping deletions in the ANT-C, we hoped to further define the genetic fine structure of this gene complex

and also to utilize overlapping deficiencies in developmental studies of the effects of the true null condition for various sets of genes within the complex.

MATERIALS AND METHODS

Flies were grown on standard cornmeal and molasses medium supplemented with Brewers yeast and bakers yeast. All crosses were done at 25°. For a full description of marker mutations and balancer chromosomes utilized, see LINDSLEY and GRELL 1968.

Induction and recovery of revertants: Revertants of the dominant mutations $Antp^{73b}$, *Hu*, *Dfd* and Scx^{W} were screened for by the following method: Males (aged 1–10 days) carrying the dominant mutation balanced with *In(3LR)TM3*, p^{p} *Sb e* were placed in gelatin capsules (40 males per capsule) and irradiated with 4000 r of X rays from a 250 kV orthovoltage Sieman Stabilipan machine. The irradiated males were then crossed to *In(3LR)TM3/In(3LR)CxD* females, with 15 males and 15 females per half-pint bottle. After 5 days the parental flies were transferred to new bottles. Within 18 days after the cross was made, the F_1 progeny carrying the irradiated dominant mutation heterozygous with *CxD* or *TM3* were scored for loss of the phenotype associated with the dominant mutation. The chromosomes carrying the dominant mutation being investigated were marked in the following ways: $Antp^{73b}$ *red e*, *Ki* pb^{4} $Antp^{73b}$, *Dfd* p^{p} *M(3)S31* and Scx^{W} *red e*. The chromosome carrying *Hu* was not marked with any other visible mutations. Each putative revertant was crossed to *CxD/TM3* to retest for the loss of the mutant phenotype and to establish a stock. Revertants were designated by the name of the original dominant mutation followed by the superscript $+RX\#$ in the numerical order in which they were recovered. Eighteen separate X-ray screens were performed.

Cytology: In the cases in which the revertant chromosome was marked with *red*, males heterozygous for the revertant chromosome and *TM3* were crossed to *red e* virgin females, and larvae with red malpighian tubules were selected for polytene chromosome analysis. In most other cases, males were crossed with virgin Ore-R females so that one-half of the larvae were heterozygous for the revertant chromosome and Ore-R.

The *Hu* mutant is associated with a double inversion which made analysis of the additional aberration present in Hu^{+RX1} difficult. To better determine the polytene band order in *Hu* and its revertant Hu^{+RX1}, the polytene chromosomes of *Hu* homozygotes and Hu^{+RX1}/Hu heterozygotes were observed. Homozygous *Hu* and Hu/Hu^{+RX1} heterozygotes survive until third instar but at a low frequency. To identify larvae of these genotypes, *Hu/TM3* and $Hu^{+RX1}/TM3$ males were crossed to Ch^{V} *red sbd/TM3* virgin females. Ch^{V} is a dominant mutation on the third chromosome which results in fat, short larvae (VALENCIA 1968). The Hu/Ch^{V} F_1 were crossed to each other, and, at the same time, Hu^{+RX1}/Ch^{V} males were crossed with Hu/Ch^{V} virgin females. From these crosses, the Hu/Hu^{+RX1} and *Hu/Hu* larvae were identified as the phenotypically nonchubby class.

To clarify the nature of the polytene band order in $Antp^{73b}$, homozygous $Antp^{73b}$ larvae were generated by crossing $Antp^{73b}$ *red e/TM3* virgin females to $X,y/y^{+}$ Y $Antp^{+}$; $Antp^{73b}$*red e/TM3* males. The y^{+} *Y* $Antp^{+}$ chromosome carries a duplication of the ANT-C due to the attachment of polytene bands 83E7-84D5 plus 100B3-100F5 to the *Y* chromosome. Homozygous $Antp^{73b}$ *red e* males, with the duplication, survived until late third instar and were detected by their red malpighian tubules.

Crosses for cytology were made in half-pint bottles and were initiated at 25°. After 3 days, the parents were discarded, and the bottles were transferred to 18°. The diet of the developing larvae was supplemented daily with a few drops of yeast suspension. The polytene chromosomes were prepared by standard squash procedures. Observations and photographs were made with a Zeiss Photomicroscope III using phase contrast.

Segregation analysis: Each revertant that appeared by cytological analysis to be a translocation was analyzed for its segregation behavior with the other chromosome involved in the translocation, simply to confirm genetically the presence of the translocation. Males from each revertant stock were crossed to *Cy/Pm*; *D/Sb* females. F_1 male progeny that were either *Pm* or *Cy* and either Revertant/*D* or Revertant/*Sb* were then crossed to Ore-R virgin females, and the segregation behavior of the Revertant chromosome with regard to the *Pm* or *Cy* chromosome *II* was followed in the F_2 generation.

Complementation and adult phenotypes: The complementation pattern of each revertant was deter-

mined for a set of EMS-induced lethal and visible mutations which had previously been isolated in screens utilizing two separate deficiencies that overlap in the ANT-C (LEWIS *et al.* 1980a,b). All revertants were tested for complementation with at least one allele from each of nine identified complementation groups which are exposed by *Df(3R)Scr* (84A2-84B1). Previous complementation analysis has determined the relationship of $Antp^{73b}$, Scx^{W} and *Hu* to other mutations in the ANT-C (LEWIS *et al.* 1980b; KAUFMAN, LEWIS and WAKIMOTO 1980), as described in the introduction.

Crosses were made in shell vials at 25°. Virgin females from each revertant stock were crossed with males from each of the EMS-induced point mutation stocks, four males and four females per vial. Parents were transferred after 4 days to new vials. A total of at least 100 progeny were scored for each cross. A revertant was defined as being lethal with a given mutation when no adult progeny heterozygous for the revertant and the mutation were recovered.

In cases in which detailed observations of adult structures were required, adult flies were observed with a Zeiss Photomicroscope III using bright-field. Flies were fixed in 70% ethanol. Pigment was removed from the eyes by boiling the flies for 10 min in 10% KOH; the heads and legs were then mounted in Gurr's mounting medium for observation. In the case of the Scx^{W} revertants, the number of teeth in the sex combs were counted in 50 male flies for each revertant stock ($Scx^{W+RX\#}/TM3$). In the cases in which complementation indicated a lesion at the *Scr* locus, all flies carrying *Scr* alleles which were viable with that revertant were examined for the number of sex comb teeth and phenotype of the proboscis. Since some revertants that were associated with deficiencies for parts of the ANT-C showed dominant proboscis defects, each deficiency was made heterozygous with Ore-R, and the heads of 20 flies heterozygous for the deficiency and Ore-R were observed with the compound microscope. Additionally, the phenotype of the proboscis was observed in heterozygotes with Ore-R and one representative point mutation from each identified complementation group. In each case the number of pseudotracheal rows and fragments of pseudotracheal rows in the proboscis was counted, and the phenotype of the labellar caps of the proboscis was noted.

RESULTS

Reversion screens

A total of 41,779 chromosomes was scored in the F_1 progeny of irradiated parents, and 17 revertants were recovered. Table 1 shows the number and frequency of revertants recovered for each dominant mutation.

Cytology

Thirteen of the 17 revertants recovered were associated with new breakpoints in the polytene interval 84A-B, previously identified as the cytological region containing the ANT-C. Figure 1 illustrates the general location of the breakpoints of these 13 revertants. The cytology of each of the 17 revertants is summarized in Table 2 and will be described in the following section.

Revertants of $Antp^{73b}$: The $Antp^{73b}$ mutation is associated with a small inversion which is difficult to see when it is heterozygous with a chromosome with a normal polytene band order. Photomicrographs of polytene chromosomes of Ore-R, $Antp^{73b}$/Ore-R and $Antp^{73b}/Antp^{73b}$ are shown in Figure 2. Apparently, a portion of the heavy 84B1,2 band has been inverted with the other breakpoint of the inversion occurring just distal to 84C5.

$Antp^{73b+RX9}$ is cytologically identical with $Antp^{73b}$. There are two deficiencies that appear cytologically identical and delete bands 84A4,5 through 84B1,2 plus material in 84C that had been juxtaposed to 84B1,2 by the inversion present in the parent chromosome. These two deficiencies, $Antp^{73b+RX3}$ and

TABLE 1

Results of screens for revertants of dominant mutations

Chromosome	No. scored	Revertants	Frequency of reversion
Dfd p^p M(3)S31	20,870	3	1.4×10^{-4}
Scx^W red e	5,652	6	1.1×10^{-3}
Hu	11,135	1	8.9×10^{-5}
$Antp^{73b}$ red e	2,043	5	2.5×10^{-3}
Ki pb^4 $Antp^{73b}$	2,079	2	9.6×10^{-4}

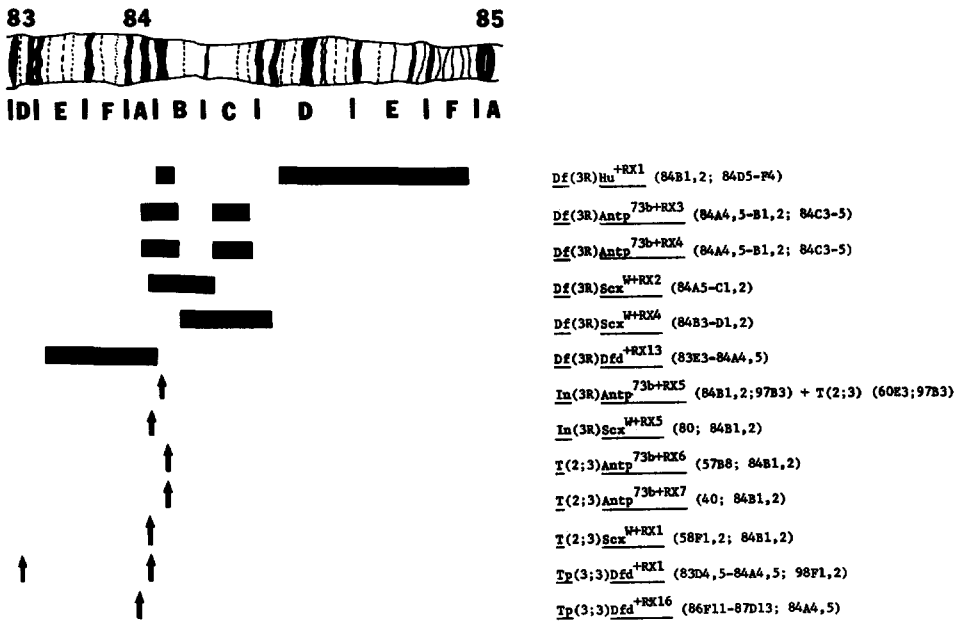

FIGURE 1.—Cytology of revertants with breakpoints in polytene region 84. Black bars indicate extent of deficiencies. The cases in which deficiencies appear to skip bands are due to the fact that these deficiencies were induced in chromosomes that contained inversions. Arrows indicate breakpoints occurring in region 84. Breakpoints outside of region 84 are given in the description of each rearrangement in Table 2.

$Antp^{73b+RX4}$, were isolated in separate screens; the former is marked with *Ki* and the latter is marked with *red e*. Both of these revertants have a reduced sex comb phenotype which is true of other deficiencies that delete 84B1,2 and also of EMS-induced point mutations at the *Scr* locus. There are two revertants that are simple reciprocal translocations: *T(2;3)$Antp^{73b+RX6}$* (57B6-8;84B1,2) and *T(2;3)$Antp^{73b+RX7}$* (40;84B1,2). One revertant is associated with three breaks which yielded an inversion plus a translocation: *In(3R)$Antp^{73b+RX5}$* (84B1,2;97B3) plus T(2;3)60E3;97B3. Finally, one revertant, *Dp(3;3)-$Antp^{73b+RX8}$* is a tandem direct repeat for bands 84D5-8;85F5-8. This tandem duplication was recovered in the second brood of F_1 progeny so that a pre-meiotic stage spermatocyte could have been the target for the irradiation.

TABLE 2

Summary of cytological analysis of parent chromosomes and revertants

Mutation	Cytology (breakpoints)
In(3R)Antp^{73b}	84B1,2;84C5,6
Df(3R)Antp$^{73b+RX3}$	84A4,5-B1,2 + 84C3-C5
Df(3R)Antp$^{73b+RX4}$	84A4,5-B1,2 + 84C3-C5
In(3R)Antp$^{73b+RX5}$	84B1,2;97B3 + T(2;3)60E3;97B3
T(2;3)Antp$^{73b+RX6}$	57B6-8;84B1,2
T(2;3)Antp$^{73b+RX7}$	40;84B1,2
Dp(3;3)Antp$^{73b+RX8}$	84D5-8;85F5-8
In(3R)Antp$^{73b+RX9}$	84B1,2;84C5,6
In(3R)Hu	84B1,2;84F4;86C7-8
Df(3R)Hu^{+RX1}	84B1,2 + 84D5-84F4
Dfd	Normal
Tp(3;3)Dfd^{+RX1}	83D4,5-84A4,5 → 98F1,2
Df(3R)Dfd^{+RX13}	83E3-84A4,5
Tp(3;3)Dfd^{+RX16}	86F11-87D14 → 84A4,5
Dfd^{+RX17}	Normal
Scx^{W}	Normal
T(2;3)Scx^{W+RX1}	58F1;84B1,2
Df(3R)Scx^{W+RX2}	84A5-84C1,2
Scx^{W+RX3}	Normal
Df(3R)Scx^{W+RX4}	84B3-84D1,2
In(3R)Scx^{W+RX5}	81(het);84B1,2
T(2;3)Scx^{W+RX6}	22D1;63A1,2 + 54A1;80-81

Presumably, such a tandem duplication could arise by breakage and rejoining of sister chromatids. In summary, one of the *Antp*^{73b} revertants has no additional visible chromosomal aberrations, one has a duplication of material outside of the 84B region, two revertants remove the 84B1,2 doublet and three revertants have breakpoints just distal to 84B1,2.

Revertants of Hu: The single *Hu* revertant that was recovered, *Hu*$^{+RX1}$, proved to be associated with deficiency. Heterozygous males carrying *Hu*$^{+RX1}$ have a reduced sex comb phenotype. Our analysis places the inversion breakpoints of *Hu* at 84B1,2, 84F4 and 86C7-8. *Df(3R)Hu*$^{+RX1}$ is a deletion for 84B1,2 plus material that is adjacent to it in the *Hu* inversion, encompassing polytene bands 84D5-84F4.

Revertants of Dfd: Four revertants of *Dfd* were recovered. (These are not numbered sequentially due to the fact that several of the initially recovered revertants did not retest.) One of these, *Dfd*$^{+RX17}$, is cytologically normal. Of the other *Dfd* revertants, two are transpositions and one is a deficiency. The *Dfd*$^{+RX1}$ reversion transposes polytene bands 83D4,5-84A4,5 to the distal end of the right arm of chromosome *3*, inserting these bands adjacent and distal to 98F1,2. In *Dfd*$^{+RX16}$, there is an insertion of polytene bands 86F11-87D14 into, or just distal to, the 84A4,5 doublet. Finally, *Dfd*$^{+RX13}$ is a deficiency that removes 83E3-84A4,5. Adult males heterozygous for *Dfd*$^{+RX13}$ have a reduced sex comb phenotype. All chromosomally aberrant *Dfd* revertants have at least one breakpoint associated with the 84A4,5 doublet. Figure 3 shows photomicrographs of the polytene chromosomes of the *Dfd* revertants.

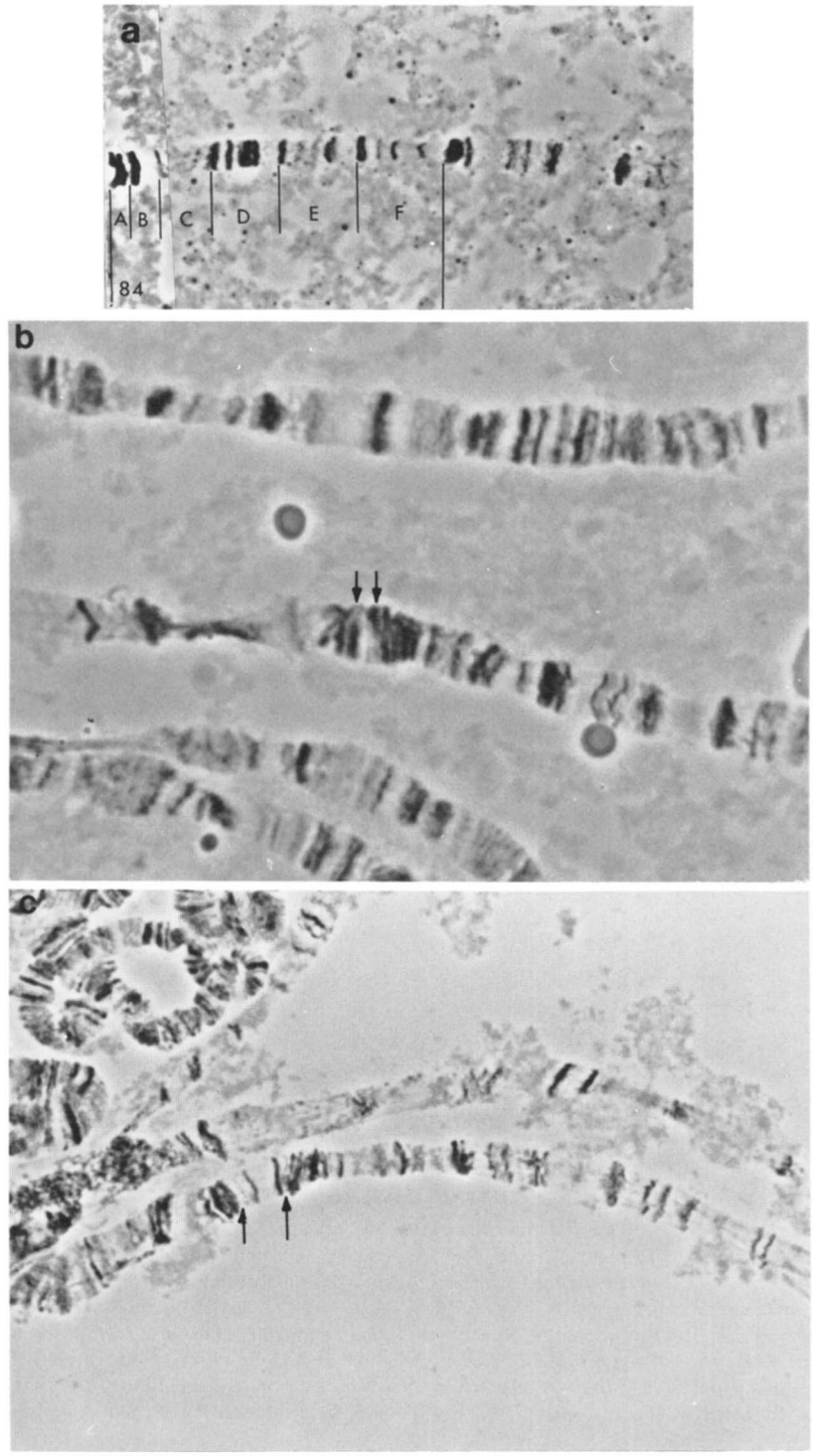

FIGURE 2.—Cytology of *Antp*^{73b}. a, Ore-R; polytene interval 84A-F. b, *Antp*^{73b}/Ore-R heterozygote. Arrows indicate inversion breakpoints at 84B1,2 and 84C5. Proximal part of *3R* is to the left. c, *Antp*^{73b} homozygote. Arrows indicate inverted material. Proximal part of *3R* is to the left.

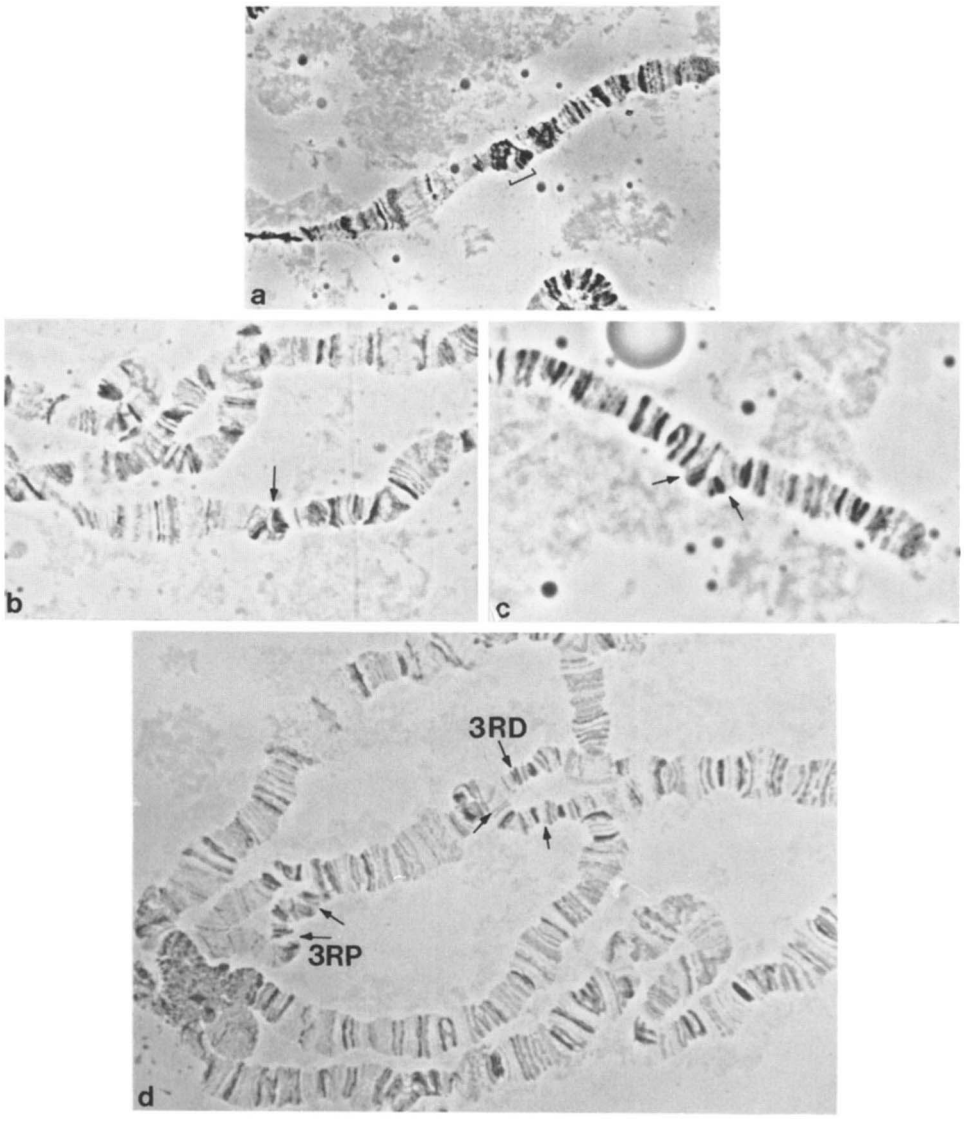

FIGURE 3.—*Dfd* revertants. All revertant chromosomes are heterozygous with Ore-R. a, *Df(3R)Dfd*$^{+RX13}$(83E3-84A4,5). Bar indicates extent of deficiency. b, *Tp(3;3)Dfd*$^{+RX1}$(83D4,5-84A4,5; 98F1,2). Proximal *3R*; arrow indicates deficiency created by transposition event. c, *Tp(3;3)Dfd*$^{+RX1}$(83D4,5-84A4,5; 98F1,2). Distal *3R*; polytene bands between the two arrows are the transposed material. d, *Tp(3;3)Dfd*$^{+RX16}$(86F11-87D13; 84A4,5). Asynapsis occurs at the site of the deficiency created by the transposition event and also at the site where the transposed material is inserted. 3RD = distal region of *3R*; 3RP = proximal region of *3R*. Single arrow at 3RD site is the site of the deficiency; the two arrows on the opposite homologue indicate the extent of the material included in the transposition. The two arrows at the 3RP site delimit the transposed material.

Revertants of Scx^{W}: The Scx^{W} revertants which contained chromosomal aberrations are shown schematically in Figure 1. One revertant, Scx^{W+RX3}, is cytologically normal. Two Scx^{W} revertants are deficiencies: $Df(3R)Scx^{W+RX2}$ deletes polytene bands 84A5-84C1,2, and $Df(3R)Scx^{W+RX4}$ removes 84B3-84D1,2 and may actually take out a fraction of 84B1,2. $In(3R)Scx^{W+RX5}$ has one breakpoint at the proximal side of 84B1,2 and a second breakpoint in the centromeric heterochromatin of *3R*. $T(2;3)Scx^{W+RX1}$ (58F1;84B1,2) is a reciprocal translocation between the right arms of chromosomes *2* and *3*; the breakpoint in the third chromosome is just adjacent and proximal to 84B1,2. Revertant Scx^{W+RX6} (22D1;63A1,2 and 54A1,2;80-81) contains two 2-3 translocations. There is no visible breakpoint in region 84, but pairing of the polytene chromosome in proximal *3R* is usually disrupted, presumably due to the *2R-3* translocation in which the third chromosome breakpont is in the centric heterochromatin. The 84B1,2-associated breakpoints of Scx^{W} revertants are either adjacent and just proximal to 84B1,2 (Scx^{W+RX1} and Scx^{W+RX5}), remove 84B1,2 (Scx^{W+RX2}) or are just distal to or within 84B1,2 (Scx^{W+RX4}). All Scx^{W} revertants have reduced sex comb phenotypes which will be described later.

Segregation analysis

In all cases, segregation analysis confirmed the presence of translocations that had been first observed cytologically.

Complementation and adult phenotypes

The complementation map resulting from crossing each revertant to representative alleles of the loci in and adjacent proximally to the ANT-C is shown in Figure 4.

Prior complementation analysis (LEWIS *et al.* 1980b) had divided the 84A-B interval into three regions: a proximal region exposed only by *Df(3R)Scr*, a middle region exposed by *Df(3R)Scr* and $Df(3R)Antp^{Ns+R17}$ and a distal region exposed by these two deficiencies and also by failure to complement $T(3;4)Antp^{Ns+R2}$. Complementation patterns with overlapping deficiencies induced in these experiments further define the proximal-distal relationships of the sites in this interval. Thus, since Scx^{W+RX2} fails to complement *pb* and mutations at the *zen* locus while it complements *EfR9*, *EfW1* and *EfW5*, the *pb* and *zen* sites must be more distal than the other three loci. The fact that Hu^{+RX1} exposes only the *Scr* and *Antp* sites is consistent with the conclusion that these two sites are the most distal ones in the ANT-C. Finally, the failure of Dfd^{+RX13} to complement *Scr* with its concomitant complementation of *Antp* indicates that *Scr* is the more proximal of these two sites. It should be noted, however, that we also have data placing the *Scr* locus to the left of or proximal to *ftz* (T. C. KAUFMAN, unpublished results). It would appear, therefore, that lesions on either side of the *ftz* locus are capable of mutating *Scr*.

In the cases of $Antp^{73b}$ and Scx^{W}, all revertant derivatives retained the recessive lethality associated with the parent chromosome. *Dfd* and *Hu* are not by themselves lethal in combination with any mutations in the ANT-C, so it was of particular interest to identify the group of alleles, if any, that revertants of

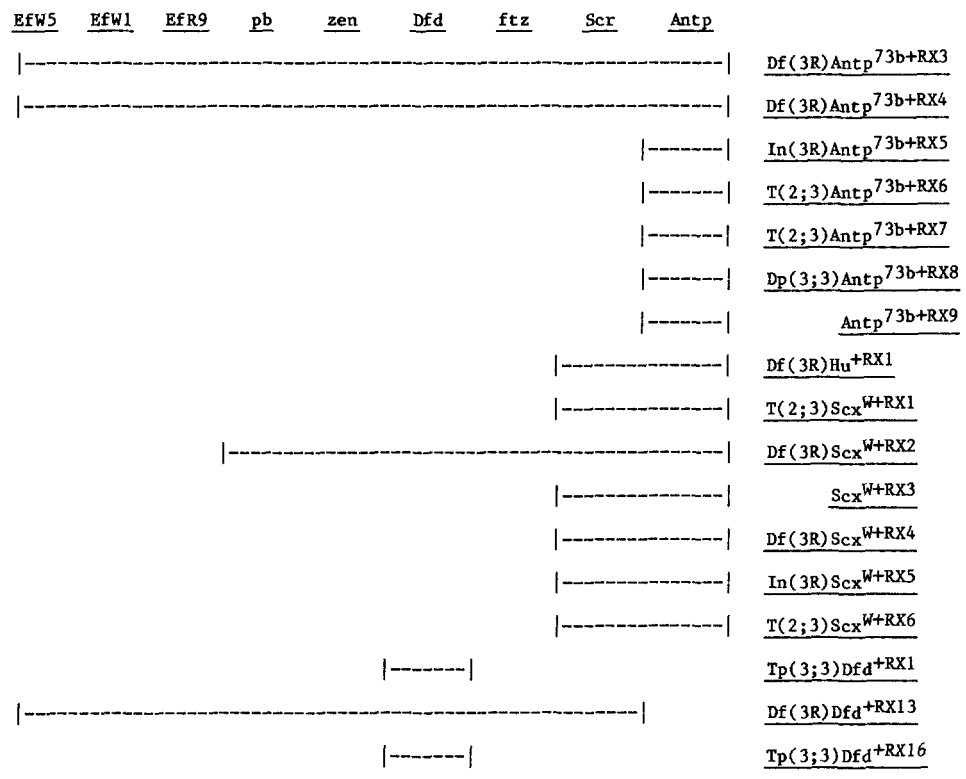

FIGURE 4.—Complementation map of revertants with loci in and adjacent to the ANT-C. Bars indicate failure to complement, defined as 0 progeny in the mutation/revertant class, when at least 100 offspring were scored. The *EfW5*, *EfW1* and *EfR9* loci are named by their mutant recovery designations. The other loci are abbreviated as follows: *pb* = proboscipedia, *zen* = zerknullt, *Dfd* = Deformed, *ftz* = fushi tarazu, *Scr* = Sex combs reduced, *Antp* = Antennapedia.

these mutations would fail to complement. If X-ray-induced reversion of a dominant mutation is due to the loss or alteration of function of a gene, then one should be able to identify the locus of a particular dominant mutation by virtue of the failure of its revertants to complement the alleles at this locus. This reasoning leads us to conclude that the complementation group represented by the *EfR3* lesion (LEWIS *et al.* 1980a) is the locus of *Dfd* since three revertants are lethal with all alleles in this group. One revertant, Dfd^{+RX17}, was not lethal with these mutations, nor was it lethal with any other mutation tested in the ANT-C. Apparently, either *Dfd* can be reverted without inducing lethality or the failure of the three revertants to complement *EfR3* results from the deletion of an adjacent vital locus unrelated to *Dfd*, whereas the inactivation of *Dfd* alone does not result in lethality. Due to the fact that two of the lethal revertants are transpositions with single breakpoints in 84A4,5, we favor the conclusion that *Dfd* and *EfR3* are allelic.

The enhancement of the *Hu* phenotype when *Hu* is placed in *trans* with

recessive lethals at the *Antp* locus had led to the conclusion (LEWIS *et al.* 1980a) that *Hu* is an allele of *Antp*. The fact that Hu^{+RX1} is lethal with both *Scr* and *Antp* lethal mutations is consistent with that conclusion. However, since only one *Hu* revertant was recovered, and it fails to complement both loci, we cannot take this as conclusive evidence for allelism. Interestingly, Hu^{+RX1} does not show reduced viability with all *Scr* alleles. The complementation of Hu^{+RX1} with various *Scr* alleles is shown in Table 3.

The Scx^{W} mutation had previously been defined as an *Antp* allele by virtue of its lethality when in combination with a majority of the then extant lethal *Antp* alleles (LEWIS *et al.* 1980a) and also because of its terminal embryonic phenotype (WAKIMOTO and KAUFMAN 1981). However, Scx^{W} has rather complex characteristics which indicate that it is either a single mutation that affects the functioning of both the *Scr* and *Antp* loci or is in actuality a double mutation with lesions at both *Antp* and *Scr*. With certain alleles of *Scr*, Scx^{W} is semilethal, whereas with other alleles it shows normal viability (Table 3). Thus, Scx^{W} is semilethal with Scr^{w17}, Scr^{w22} and *Msc*, whereas it is viable in combination with Scr^{r18}, Scr^{d8} and Scr^{k6} (Table 3). Because of this complex complementation pattern of Scx^{W} with the *Scr* locus, complementation of the Scx^{W} revertants was done with all of the alleles mentioned. In cases in which the mutation/reversion class survived, the number of sex comb teeth on the prothoracic leg of males was observed. Also, since mutations at the *Scr* locus (*r18* and *w22*) which survive with a deficiency for the ANT-C (*Df(3R)Scr*) show an abnormal proboscis in which the labial palps have a reduced number of pseudotracheal rows and unusual bristles (LEWIS *et al.* 1980a), the phenotype of the proboscis was also observed in these cases. These results are shown in Table 3.

These complementation results show that lesions at the *Scr* locus always disturb the morphology of the pseudotracheal rows in the proboscis and sometimes alter the labellar caps. LEWIS *et al.* (1980b) described the proboscis defects of hemizygous *Scr* alleles (*r18* and *w22*) as a transformation of labial palp to maxillary palp. The results of the complementation presented here indicate that the labial to maxillary transformation is the most extreme phenotype witnessed in a continuum which has as its weakest manifestation a slight reduction in pseudotracheal rows. As the number of pseudotracheal rows is decreased further, the labellar caps appear slightly squarish in shape and have more bristles than are normally present. When the number of pseudotracheal rows is less than three, the labellar lobes resemble maxillary palps. The effect on the prothoracic leg approximately parallels the effect on the proboscis, with varying degrees in the extent of transformatin of prothoracic to mesothoracic leg. The reduction in sex comb teeth is accompanied by loss of transverse rows in the basitarsus and tibia and loss of long bristles on the posterior aspect of the femur, making the entire chaetotaxy in the most extreme cases like that of a mesothoracic leg.

Prior analysis of *Scr* alleles led to the conclusion (LEWIS *et al.* 1980b) that the alleles varied in their degree of expression of Scr^{+} product. The apparent relative amounts of Scr^{+} activity in the revertants recovered in this study can be ordered as follows:

TABLE 3

Results of the complementation analysis of revertants that have Scr *lesions with alleles at the* Scr *locus*

	Scr locus mutation																	
	Scr^{r18}			Scr^{w22}			Scr^{d8}			*Msc*			Scr^{k6}			Scr^{w17}		
Revertants	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c	a	b	c
Scx^{W}	133	6.1	4.9	17	4.9	4.1	62	2.9	5.3	14	0.2	5.3	54	1.8		3	≤2	
Scx^{W+RX1}	110	4.9	3.9	64	4.9	3.8	71	3.4	1.3	0			0			0		
Scx^{W+RX2}	68	1.0	1–2	0			0			0			0			0		
Scx^{W+RX3}	0			0			0			0			0			0		
Scx^{W+RX4}	107	5.0	5.0	77	2.4	5.6	61	0.5	4.2	12	0	3.2	46	0	5.0	3	0	3.8
Scx^{W+RX5}	0.39	0	2–3	0			0			0			0			0		
Scx^{W+RX6}	0.62	1	2–3	0			0			0			0			0		
Hu^{+RX1}	66	4.4	5.6	94	2.0	1–5	22	0.2	3.8	0			0			0		
Dfd^{+RX13}	0			0			0			0			0			0		

Percentage values in columns marked a are percent viability, defined as the observed number of progeny of the mutation/revertant class, divided by the expected number in that class. Columns marked b show the average number of sex comb teeth observed in males of the mutation/revertant class. Columns marked c list the average number of pseudotracheal rows for each half-proboscis in this same genotype. The proboscis data was not obtained for Scr^{k6}/Scx^{W} and Scr^{w17}/Scr^{W}.

$$\begin{matrix} Scr^{-} \\ Df(3R)Scx^{W+RX2} \\ Scx^{W+RX3} \\ In(3R)Scx^{W+RX5} \\ T(2;3)Scx^{W+RX6} \\ Df(3R)Dfd^{+RX13} \end{matrix} < \begin{matrix} T(2;3)Scx^{W+RX1} \\ Df(3R)Hu^{+RX1} \end{matrix} < \begin{matrix} Scx^{W} \\ Df(3R)Scx^{W+RX4} \end{matrix} < Scr^{+}$$

Dominant phenotypes of the ventral pro-, meso- and metathoraces of flies carrying revertants of Scx^{W}: As mentioned previously, Scx^{W} has two components to its phenotype: a dominant reduction in the number of sex comb teeth on the prothoracic legs and a dominant extra sex comb phenotype in which sex combs are observed on the meso- and metathoracic legs. These two components will be referred to as the Scr and Scx components, respectively.

Table 4 shows the average number of sex comb teeth observed on the prothoracic, mesothoracic and metathoracic legs of males of each $Scx^{W+RX\#}$/*TM3* stock. These data show that four of the Scx^{W} revertants are not complete revertants to wild type: Scx^{W+RX1}, Scx^{W+RX3}, Scx^{W+RX5} and Scx^{W+RX6}. These four revertants still show a slight penetrance and expressivity of the *Scx* phenotype, however, they also exhibit new lethal interactions with *Scr* alleles (Table 4) relative to the Scx^{W} parent chromosomes. The other two revertants, Scx^{W+RX2} and Scx^{W+RX4}, are complete revertants for the Scx component. Of these, Scx^{W+RX2} also shows new lethal interactions with *Scr* alleles, indicating an alteration in the Scr component. Flies of the genotype Scx^{W+RX2}/*TM3* have a more extreme Scr phenotype than do Scx^{W+RX4}/*TM3* flies. Thus, it appears that it is possible to revert Scx^{W} in two different ways (or simultaneously in both ways): by further altering the functioning of the *Scr* locus, yielding a more extreme Scr component to the mutation, or by reverting just the Scx component. Only revertant Scx^{W+RX4} does the latter.

Effects of hypoploidy on the proboscis: The dominant effects on the adult proboscis of each deficiency was observed in flies heterozygous for the deficiency and Ore-R third chromosomes. Also, a representative point mutation from each locus in and adjacent to the ANT-C was observed heterozygous with Ore-R. Table 5 shows the average number (based on 20 flies for each genotype) of pseudotracheal rows for each half-proboscis, plus the range in number of pseudotracheal rows observed, for various chromosomes in combination with Ore-R. Since the Dfd^{+RX13} chromosome carried *M(3)S31*, the pseudotracheal rows in the proboscis of *Ki M(3)S31*/Ore-R flies were observed in order to assess any independent effects exerted by *M(3)S31*. A duplication carrying the ANT-C attached to the *Y* chromosome was included in one case to determine whether the duplication rescued the dominant effect of the deficiency on the proboscis. A Kolmogorov-Smirnov test was performed to assess the level of statistical significance for each deficiency genotype relative to the Ore-R control.

Deficiencies for the entire or a majority of the ANT-C (*Scr* and Dfd^{+RX13}) show a significant alteration in the morphology of the proboscis. This phenotype is shown in the photomicrographs in Figure 5. In addition to reducing the number of pseudotracheal rows, fragments of remaining pseudotracheal

TABLE 4

Number of Sex Comb Teeth on Legs of Males Carrying Revertants of Scx^W

Genotype	Prothoracic leg	Mesothoracic leg	Metathoracic leg
CxD/TM3	11.40 (10–13)	0	0
$Scx^W/TM3$	8.68 (6–10)	3.69 (0–10)	0.71 (0–6)
$Scx^{W+RX1}/TM3$	7.99 (6–10)	0.03 (0–1)	0
$Scx^{W+RX2}/TM3$	6.65 (5–8)	0	0
$Scx^{W+RX3}/TM3$	7.30 (5–9)	0.51 (0–5)	0.09 (0–2)
$Scx^{W+RX4}/TM3$	7.57 (6–9)	0	0
$Scx^{W+RX5}/TM3$	6.06 (5–7)	0.28 (0–2)	0.04 (0–2)
$Scx^{W+RX6}/TM3$	5.99 (4–8)	0.26 (0–3)	0.01 (0–1)

The value for each leg represents the mean number of teeth on 40 legs. The values in parentheses are the range of the number of teeth.

rows are usually seen, and the labellar caps have long extra bristles on the ventral surface. Occasionally, very stout bristles are seen in the region between the third and fourth pseudotracheal rows. The pseudotracheal rows that are eliminated or fragmented are most often the fourth, fifth and sixth rows (counting the most distal, outer row as the sixth row), although this effect can extend up to and include the third row. Occasionally, the fragmented rows are seen to fuse at one end with a neighboring pseudotracheal row. The smallest deficiency (in terms of the number of ANT-C loci that are exposed by the deficiency) that has a significant dominant effect is $Df(3R)Scx^{W+RX2}$. Neither $Df(3R)Antp^{Ns+R17}$/Ore-R nor Hu^{+RX1}/Ore-R individuals showed significant alterations in the proboscis. None of the point mutations tested exhibited significant dominant effects on the proboscis.

DISCUSSION

The results of these experiments lead us to conclude that Scx^W, *Dfd*, *Hu* and $Antp^{73b}$ are mutations that cause their effects by a gain-of-function relative to wild type since deficiencies were recovered as revertants of each of these mutations. The cytological breakpoints of revertants containing chromosomal aberrations indicate that each of these mutations resides within polytene band limits 84A4,5-84B1,2. Specifically, the common breakpoints shared by each set of revertants indicate that Scx^W, *Hu* and $Antp^{73b}$ are associated with 84B1,2, and *Dfd* is associated with 84A4,5. The proximal breakpoint of $Df(3R)Scx^{W+RX2}$ is within 84A4,5, and the distal breakpoint of *Df(3R)Scr* is within 84B1,2. The overlap of these two deficiencies cytologically is maximally the interval 84A4,5-84B1,2. Genetically, the overlap of these two deficiencies exposes six loci of the ANT-C: *pb*, *zen*, *Dfd*, *ftz*, *Scr* and *Antp*. This situation appears to be an exception to the one gene-one band rule since six complementation groups reside within two heavy polytene bands.

The characteristics of revertants of $Antp^{73b}$ support a previous conclusion regarding this mutation. A majority of chromosomally aberrant revertants of $Antp^{73b}$ cytologically map to 84B1,2, as do chromosomally aberrant *Ns* rever-

TABLE 5

Dominant effects of ANT-C deficiencies on proboscis morphology

Genotype	Average number of pseudotracheal rows	Range of pseudotracheal rows	Significant at 0.01 level
Ore-R	6	6	No
Df(3R)Hu^{+RX1}/Ore-R	6.02	6–7	No
Df(3R)Ns^{+R17}/Ore-R	6	6	No
Df(3R)Scx^{W+RX2} *red e*/Ore-R	3.47	2–5	Yes
Df(3R)Scr p^{p} *e*^{s}/Ore-R	4.38	2–5	Yes
Df(3R)Dfd^{+RX13} *p*^{p} *M(3)S31*/Ore-R	4.98	3–6	Yes
Ki M(3)S31/Ore-R	5.85	5–6	No
Ki M(3)S31/Df(3R)Scr p^{p} *e*^{s}	3.50	1–5	Yes
y^{+} *Y Antp*$^{+}$; *Dfd*$^{+RX13}$ *p*^{p} *M*/Ore-R	5.72	5–6	No
Antp^{w10} *red e*/Ore-R	6	6	No
Scr^{r18} *p*^{p} *cu*/Ore-R	6.02	6–7	No
Scr^{w17}/Ore-R	6.02	5–7	No
ftz^{w20}/Ore-R	6	6	No
Dfd^{r11} *Ki p*^{p}/Ore-R	6	6	No
zen^{w36}/Ore-R	6	6	No
Ki pb^{5} *p*^{p}/Ore-R	5.78	5–6	No
pb^{4}/Ore-R	5.98	5–6	No
EfR9/Ore-R	6	6	No
EfW1/Ore-R	6	6	No
EfW5/Ore-R	6	6	No

The average number of pseudotracheal rows per half-proboscis is recorded for 20 flies of each genotype. The Ore-R control shows that the normal number of rows is six. Flies of the genotype *Ki M(3)S31/Df(3R)Scr p*^{p} *e*^{s} were included as a control to determine whether there is an interaction between *M(3)S31* and a deficiency for the ANT-C, since the chromosome carrying *Df(3R)Dfd*$^{+RX13}$ also carries *M(3)S31*. *Dp(Y;3)y*$^{+}$ *Y Antp*$^{+}$ carries a duplication for the ANT-C; it was incorporated in one genotype to determine whether it rescues the dominant effects produced by a deficiency for the ANT-C. The last column on the right indicates whether a given genotype produced an average number of pseudotracheal rows which was significantly different from the wild-type (Ore-R) condition. A two-tailed Kolmogorov-Smirnov test was used to assess statistical significance. This same test showed that there was no significant difference between *Ki M(3)S3/Df(3R)Scr p*^{p} *e*^{s} flies and *Df(3R)Scr*/Ore-R flies, indicating that *M(3)S31* does not interact with a deficiency for the ANT-C to alter this phenotype.

tants, strengthening the conclusion from previous reversion studies that *Antp* and *Ns* are allelic (DENELL 1972a,b, 1973; DUNCAN and KAUFMAN 1975).

The most interesting and novel aspects of these experiments are the insights the revertants provide into the natures of the *Scx*^{W} and *Dfd* mutations. Previous analysis led to the suggestion (WAKIMOTO 1981) that the complex characteristics of *Scx*^{W} may be due to either a single mutation in a control site that regulates both *Scr*$^{+}$ and *Antp*$^{+}$ or *Scx*^{W} may actually represent two separate mutations: one at the *Scr* locus and one at the *Antp* locus. These alternatives attempt to account for the seemingly disparate phenotypes of *Scx*^{W}. Adult flies carrying *Scx*^{W} have a two-component phenotype: the Scr phenotype that is due to a partial transformation of ventral prothorax to ventral mesothorax, and the Scx phenotype in which sex combs are produced on the mesothoracic and metathoracic legs due to a partial transformation of those segments to pro-

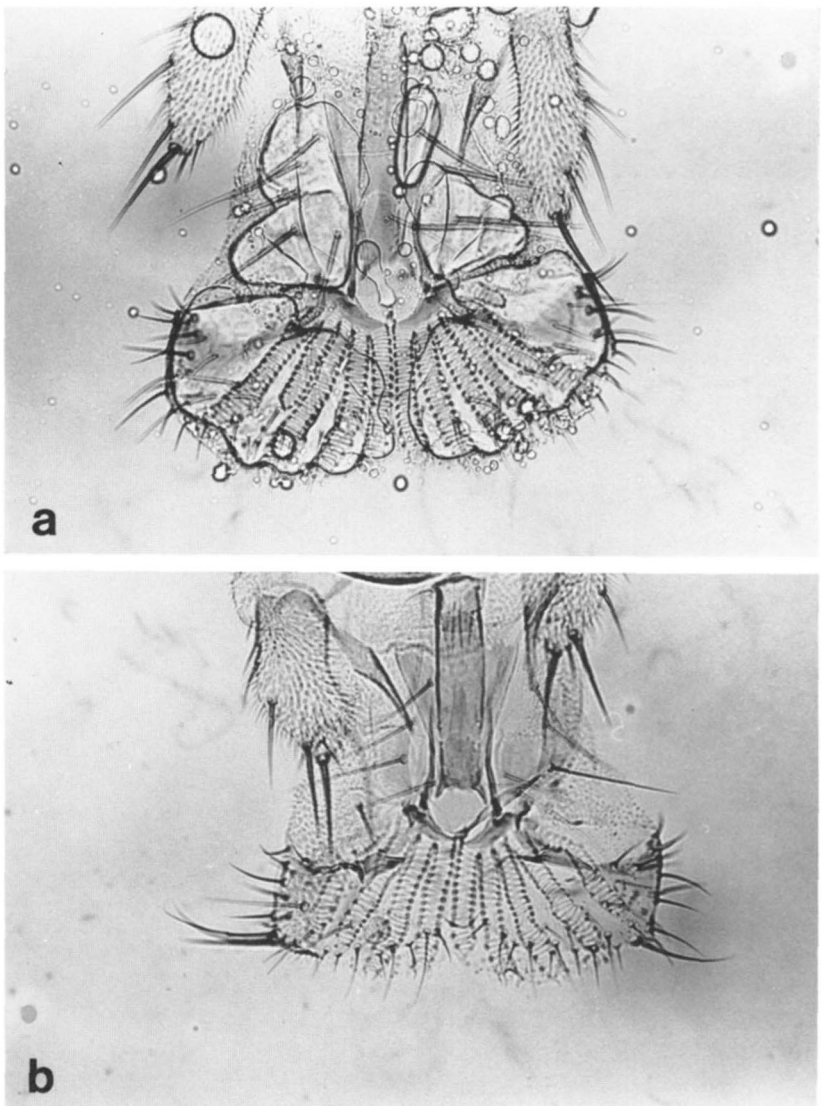

FIGURE 5.—Dominant effects of deficiencies on proboscis morphology. a, *Df(3R)Scr/Ore-R* proboscis. Left side has four pseudotracheal rows and two fragments; right side has five rows and one fragment. ×220. b, *Df(3R)Dfd*$^{+RX13}$*/Ore-R* proboscis. The left and right sides have four and five pseudotracheal rows, respectively. The labellar caps have long bristles not normally present. ×220.

thorax. In addition to the adult phenotypes just mentioned, *Scx*^{W} is a recessive lethal at the *Antp* locus, and the phenotype of lethal embryos has been interpreted as being due to loss of *Antp*$^{+}$ function (WAKIMOTO and KAUFMAN 1981). Observation of adult flies with a doubly mutant recombinant chromosome, *Scr*^{w17} *Scx*^{W} (P. FORNILI, personal communication), reveals the following facts: *Scx*^{W}/*Scr*^{w17} flies do not show the Scx phenotype, whereas *Scr*^{w17} *Scx*^{W}/Ore-R flies do have an Scx phenotype, albeit less expressive than the original *Scx*^{W}

mutation. This suggests that the Scx phenotype is dependent on dosage at the *Scr* locus. Since the Scx phenotype appears to be dependent on dosage at the *Scr* locus, it was hypothesized that the Scx phenotype is due to expression of Scr^+ in the ventral meso- and metathoraces where it is not normally expressed (WAKIMOTO 1981).

Three of the revertants recovered in this study (recall that only the Scx phenotype was used to initially identify revertants), Scx^{W+RX3}, $In(3R)Scx^{W+RX5}$ and $T(2;3)Scx^{W+RX6}$, were lethal or semilethal with all *Scr* alleles tested. These revertants were only partial revertants for the Scx phenotype and had enhanced Scr phenotypes. These revertants appear to be due to induced mutations at the *Scr* locus, leading to complete inactivation of Scr^+, resulting in a suppression of the Scx phenotype due to a lower amount of Scr^+ activity.

In the case of revertant $Df(3R)Scx^{W+RX4}$, the dominant Scx phenotype was completely reverted, whereas the Scr phenotype was unchanged. This revertant shows the same complementation pattern with *Scr* alleles as that shown by Scx^W. This suggests that the Scx and Scr phenotypes seen in Scx^W are genetically separable. Furthermore, since $Df(3R)Scx^{W+RX2}$ also completely reverts the Scx phenotype, the cytological location of this dominant gain-of-function lesion must lie in the overlap of $Df(3R)Scx^{W+RX2}$ and $Df(3R)Scx^{W+RX4}$ in the interval between the distal edge of 84B1,2 and 84C1,2.

Finally, $T(2;3)Scx^{W+RX1}$ is a particularly interesting revertant which appears to alter both the Scr and Scx phenotypes. This revertant has depressed function of *Scr* relative to Scx^W, as indicated by the fact that it is lethal with *Scr* alleles with which Scx^W is viable. Since $T(2;3)Scx^{W+RX1}$ is viable with some *Scr* alleles, it appears to have more *Scr* function than do Scx^{W+RX3}, $In(3R)Scx^{W+RX5}$ and $T(2;3)Scx^{W+RX6}$. If the reversion event in $T(2;3)Scx^{W+RX1}$ were due simply to reduced *Scr* function, then it should be a partial revertant for the Scx phenotype with a stronger Scr phenotype than that seen in the other partial revertants. However, this revertant has an extreme suppression of the Scx component: sex comb teeth were never seen on the metathoracic legs, and only three of 100 mesothroacic legs had one sex comb tooth on each leg. Therefore, $T(2;3)Scx^{W+RX1}$ appears to alter both the Scx and Scr components of Scx^W. It may be that both the linear integrity of the chromosome and also its ability to pair with its homologue are elements that affect the expression of Scx^W and that this translocation disrupts these phenomena. This suggestion is supported by another Scx^W revertant involving translocations. $T(2;3)Scx^{W+RX6}$ has two 2-3 translocations, neither of which is broken in the 84A-B region. However, due to the breakpoint in the centric heterochromatin, the base of *3R*, including 84A-B, is usually asynapsed in polytene cells. The importance of pairing of homologues for gene expression has been demonstrated in the cases of transvection at the bithorax complex (LEWIS 1964), the decapentaplegic locus (GELBART 1982) and the zeste-white interaction (JACK and JUDD 1979).

In summary, the genetic and cytological characteristics of the revertants of Scx^W provide the following information. First, since the Scx phenotype could be reverted, it is due to a dominant gain-of-function component of Scx^W. In no case was the Scr component reverted, but in some cases it became more

extreme than the parent chromosome, indicating that the Scr phenotype of Scx^W is due to a loss-of-function.

The genetics and cytology of the *Dfd* revertants have led us to conclude that *Dfd* is indeed a mutation in the ANT-C. *Dfd*, like *Hu* and *Ns*, is homozygous viable. The phenotype produced by *Dfd* is not clearly homoeotic. Scanning electron micrographs of lethal embryos hemizygous for the various alleles at the *Dfd* locus (*r11*, *w6*, *r3* and *w21*) show evidence of abnormal development of the maxillary and mandibular lobes (R. TURNER and T. KAUFMAN, unpublished results). Evidently, Dfd^+ is needed for the normal development of these embryonic head segments.

One *Dfd* revertant, Dfd^{+RX17}, is not lethal with alleles at the *Dfd* locus. This is the only case of reversion of a dominant mutation in the ANT-C that is not associated with lethality. This indicates that it is apparently possible to revert *Dfd* without incurring a complete loss of function of Dfd^+. Cytologically, Dfd^{+RX17} is like *Dfd* p^p *M(3)S31* (that is, it still carries the deficiency associated with *M(3)S31* but has incurred no new chromosome rearrangements).

Our analysis of the dominant effects of ANT-C deficiencies on the proboscis shows that hypoploidy for portions of the ANT-C results in an extreme reduction in the number of pseudotracheal rows and bristles on the labial palps. When two *pb* alleles were examined for similar dominant effects, no statistically significant effect was found, although occasionally flies were found with only five pseudotracheal rows or with fusions between the fifth and sixth pseudotracheal rows. The results of our complementation analysis of several of the recovered revertants with *Scr* mutations show that loss of function of Scr^+ results in a recessive reduction in number of pseudotracheal rows. One of us (KAUFMAN 1978) previously proposed that the recessive phenotypes of *pb* alleles may reflect varying degrees of function of pb^+ in different mutant *pb* alleles. The fact that deficiencies that delete both *pb* and *Scr* significantly affect the number of pseudotracheal rows in the proboscis in a dominant fashion supports the hypothesis that normal mouthpart development is sensitive to the dosage of these loci. This conclusion is further supported by the fact that a duplication for the ANT-C (y^+YAntp^+) rescues the deleterious dominant effects of a deficiency. Since none of the point mutations tested for dominant effects showed the extreme proboscis defects associated with a deficiency for the ANT-C, it is possible that the point mutations tested were not nulls or that the deficiencies remove other units of genetic functioning. Another possible explanation of these results is that deficiencies which include both the *pb* and *Scr* loci, as do $Df(3R)Dfd^{+RX13}$, *Df(3R)Scr* and $Df(3R)Scx^{W+RX2}$, may have a dominant effect not seen with individual point mutations for either locus alone.

The cytogenetic data presented in this study demonstrate that the adult Scx and Scr phenotypes produced by Scx^W are genetically separable. We propose that the complex nature of Scx^W is due to two components: a more distal regulatory element which is responsible for the gain-of-function Scx phenotype and a more proximal genetic lesion which results in partial suppression of the *Scr* locus. The mutant regulatory element appears to cause activation of the *Scr* locus in the wrong segments, resulting in the Scx phenotype. A plausible

hypothesis is that the normal function of this regulatory site is to activate the *Scr* locus in the prothorax. In Scx^W, this regulation is disturbed such that Scr^+ is not properly activated in the ventral prothorax but is expressed in the ventral mesothorax and metathorax. According to this hypothesis, the activation of Scr^+ must occur in *trans*, since Scr^{w17} $Scx^W/+$ has an Scx phenotype, whereas Scx^W/Scr^{w17} does not. All of the Scx^W revertants retained the recessive *Antp* lethality associated with the parent chromosome. If the dominant adult phenotypes of Scx^W are due to faulty regulation of the *Scr* locus, then a full explanation of the nature of Scx^W will require an understanding of how the mutational event that altered *Scr* regulation also resulted in an apparent inactivation of the *Antp* locus.

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