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Cell lineage of homeotic mutants of *Drosophila*

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[Plates 1–3]

The homeotic genes specify the development of specific groups of precursor cells. They establish the correct state of determination of the different primordia.

Cell lineage analysis has been particularly useful in studying the mode of action of homeotic genes. The main findings are: (i) most, perhaps all, the homeotic genes are required by every cell of the corresponding primordium (that is, they are cell autonomous); (ii) they act on anatomical units defined by compartment boundaries and including one or more compartments, (iii) most, but not all, homeotic genes are required until the end of the larval period; (iv) the homeotic genes act in combination so that the appropriate development of a given primordium may be established by the contribution of several homeotic genes.

Introduction

The techniques of marking individual cells are very powerful tools for the study of development. They allow a critical comparison between the rules governing development of an entire blastema and its constituent cells and permit us to establish whether developmental properties are controlled at the cellular or supracellular level.

In *Drosophila*, cell lineage analysis has been used ever since Stern (1935) recognized the importance of these techniques in studying the effects mutations have on the behaviour of individual cells. Perhaps the most useful lineage technique is that of X-ray induced mitotic recombination, originally developed by Becker (1957). It has the critical advantage that because the event of mitotic recombination follows immediately after the irradiation, this time marks the moment of clone initiation (figure 1). The important consequence of this is that one can label individual cells at any desired time of development. By using this method it has been possible to determine the main developmental parameters of most epidermal derivatives (García-Bellido 1968; Bryant & Schneiderman 1969; García-Bellido & Merriam 1971 *a*, *b*; see García-Bellido & Ripoll (1978) for a review) and of some internal structures (Lawrence 1982). In addition, by using a technique that allows marked cells to overgrow their neighbours (Morata & Ripoll 1975), it was found that the body of the fly is divided into precisely defined areas which derive from specific groups of precursor cells or polyclones (Crick & Lawrence 1975) that are called compartments (García-Bellido *et al.* 1973; 1976). Each segment of the body is made of two compartments, an anterior and a posterior one. This division is established early in embryogenesis (Steiner 1976; Lawrence & Morata 1977) at or shortly after the blastoderm stage.

The homeotic mutants alter the process of normal determination of specific groups of precursor cells (Morata & Lawrence 1977 *a*) resulting in the substitution of one organ by

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another. The homeotic genes are considered to act by triggering major developmental processes which eventually determine the differentiation of cells and organs. Cell marking techniques are of great use in studying homeotic genes as they permit the study of the mode of action of genes at the level of individual cells. They are also used to define the areas of the body where a given homeotic gene is necessary for the normal pattern.

There are two classes of lineage experiments that can be done with homeotic mutants: (i) production of marked mutant clones for the homeotic gene in question in a non-mutant fly; (ii) production of marked clones in mutant flies. In this article we review the evidence obtained with experiments of both types and highlight the main findings.

Production of mutant clones in non-mutant flies

Most homeotic mutants are recessive and therefore it is possible to construct heterozygous flies that show no sign of homeotic transformation. By using mitotic recombination methods as those shown in figure 1 one can generate marked clones which are also homozygous for the homeotic mutant. One can study the response of the cells to the elimination of the wildtype

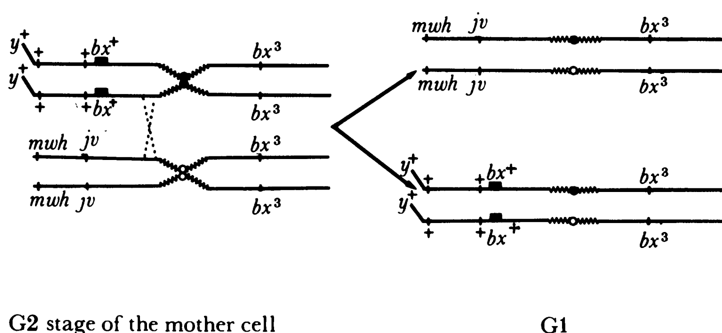

FIGURE 1. Scheme of mitotic recombination used to generate mutant bx^3/bx^3 clones in a fly with normal segmental pattern (after Morata & García-Bellido 1976). The presence of a bx^+ duplication covers the bx^3 phenotype but after mitotic recombination in the proximal part of the left arm of the third chromosome, one of the resulting cells loses the bx^+ duplication. This cell will generate a clone homozygous mutant for bx^3 and at the same time labelled with the markers *y*, *mwh* and *jv*.

gene in different developmental periods. By using this approach García-Bellido & Santamaría (1972) first investigated the requirements of the *engrailed* gene in the wing imaginal disc. Its mutations transform the posterior region of the wing and legs into the corresponding anterior region of the same appendages. They found that even clones generated very late in the proliferation period of the disc show the mutant trait. These results indicated that the normal function of *engrailed* is required until the third larval period and also that the gene is cell autonomous, that is, every cell has to make its own gene product since there is no rescue from cells in the vicinity. This example illustrates the type of information one can extract from this class of experiments. Most of the homeotic genes have been studied in this way: the bithorax complex (Morata & García-Bellido 1976; Morata & Kerridge 1981; Sánchez-Herrero *et al.* 1985), *spineless-aristapedia* (Postlethwait & Girton 1974; Morata & Lawrence 1979), *Sex combs reduced* (Struhl 1982), *Antennapedia* (Struhl 1981*a*), *wingless* (Morata & Lawrence 1977), *trithorax* (Ingham 1981), *Polycomb* (Struhl 1981*b*). The general conclusion is that they are cell

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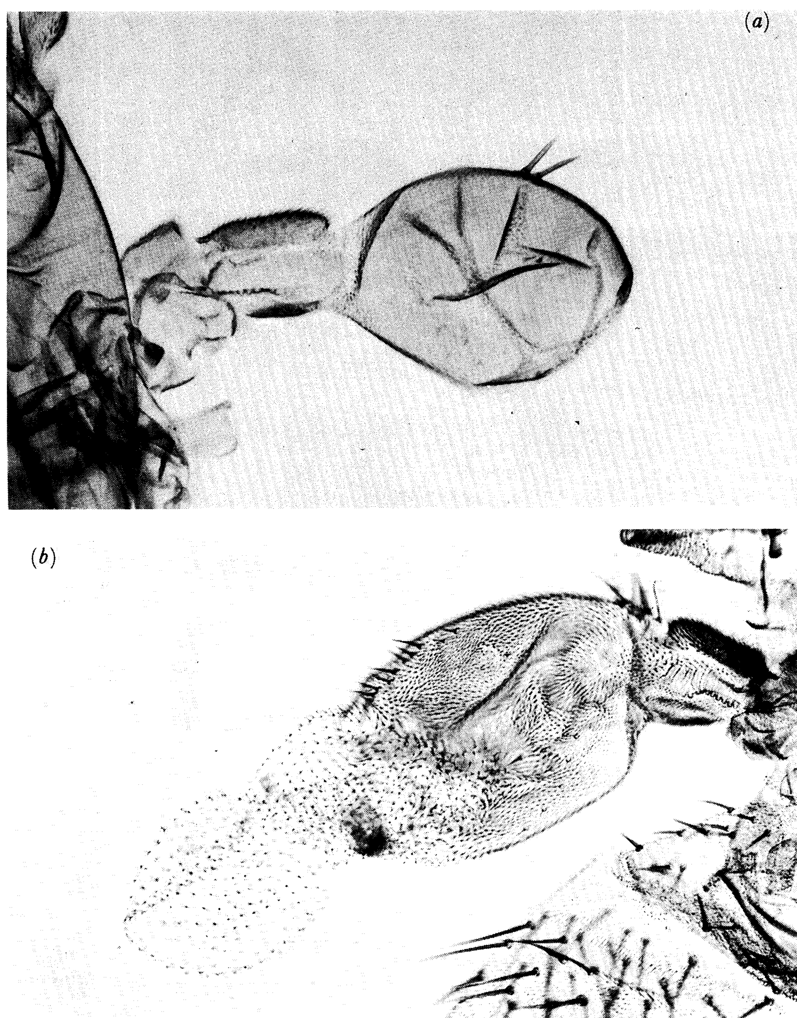

FIGURE 2. Cell autonomy of homeotic genes. a) small bx^3 homozygous clone in the haltere generated in the third larval period. It consists of two bristles typical of the anterior margin of the wing. The cells show the mutant phenotype surrounded by wildtype haltere cells. b) a larger Ubx^- clone showing differentiation of typical wing trichomes in the haltere.

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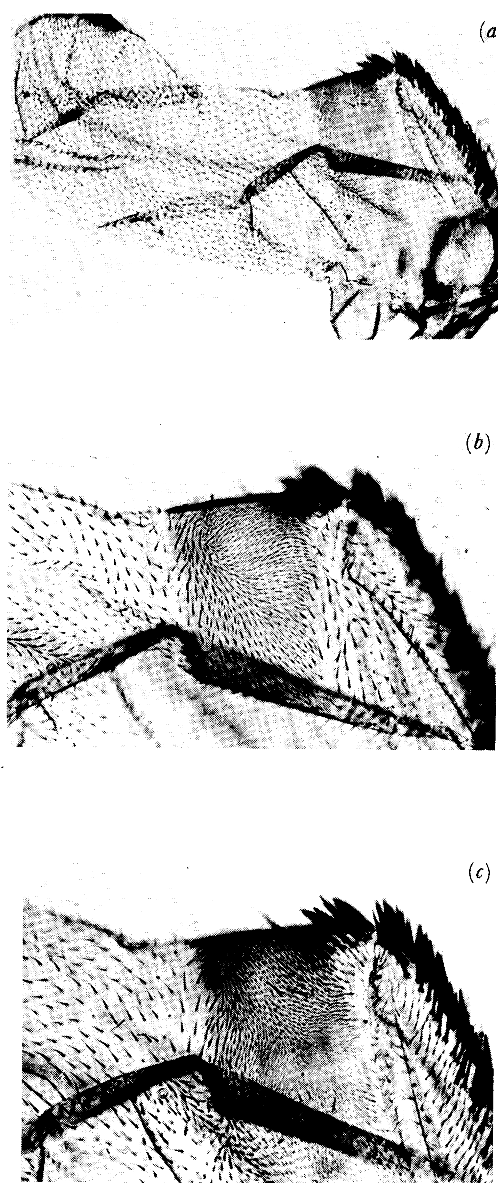

FIGURE 3. A typical Cbx^1 homozygous wing appendage. (*a*) Entire appendage, (*b*) and (*c*) dorsal and ventral views of the same structure. Notice the sharp distinction between haltere and wing territories. In this case the line separating wing and haltere runs in almost exactly homologous positions in the dorsal and ventral areas. Clones generated in a mosaic appendage like this can extend to both wing and haltere territories even if initiated late in larval development (Morata 1975).

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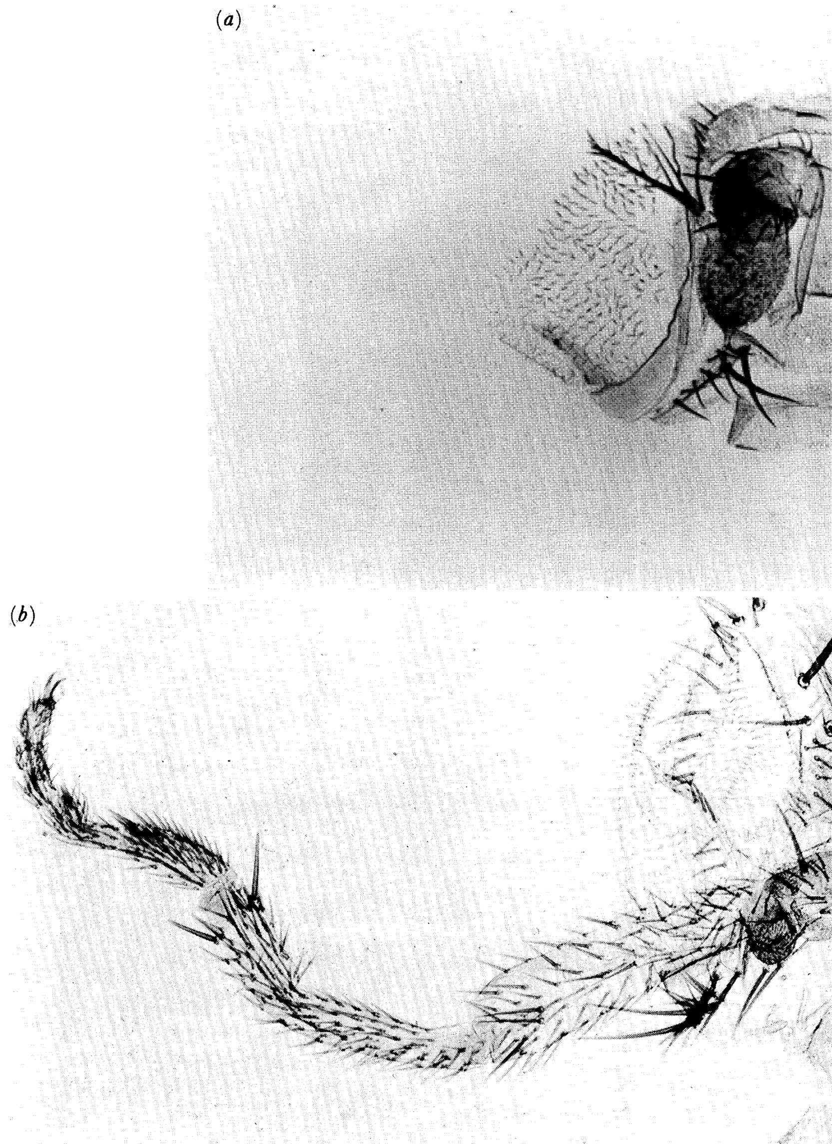

FIGURE 4. Head of an *Antp*[73] fly (*b*) showing the transformation of an antenna into a leg of mesothoracic type. A normal antenna is shown for comparison (*a*). In spite of the obvious morphological differences between the two appendages the time of establishing of the anteroposterior boundary is the same. By contrast, in the normal mesothoracic leg the anteroposterior boundary is established much earlier (Morata & Kerridge 1982, see text).

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autonomous (excepting *wingless*) and that the period of activity extends to a late phase of the larval life.

The cell autonomy of most homeotic genes is worth emphasizing; if the pattern-forming genes have to be expressed in every individual cell, it follows that the final pattern is the result of specific interactions among the cells of the population. A similar conclusion can be drawn from grafting experiments (Haynie & Bryant 1976); the differentiation of the distinct fragments of the wing disc depend on local interactions between cells. Since these genes are responsible for the state of determination of specific groups of cells, these experiments indicate that the maintenance of their determination (and hence the final pattern) depends on normal homeotic function until the late phase of development and in each individual cell (figure 2, plate 1).

The *wingless* gene appears to be the exception in that it has been reported to be non-autonomous during the larval period (Morata & Lawrence 1977*b*). However, some *wingless* mutants have been recovered as mosaics (Babu 1977) indicating that the phenotype can be expressed autonomously. It is a possibility that *wingless* is active exclusively in early development (it shows an early embryonic phenotype (Nüsslein-Volhard & Wieschaus (1980)) and the lack of autonomy later simply reflects that its function is no longer necessary. Alternatively, *wingless* may implement a cooperative decision affecting a set of polyclones as individual units in which case a few mutant cells of the clone would be rescued by the majority of normal ones.

The generation of mutant clones in a non-mutant fly also allows for the precise definition of the realm of action (the part of the body where the gene is necessary) for a given homeotic gene. When entire flies are mutant for a homeotic gene there are often secondary consequences which obscure the original topological effect of the mutation. This is particularly clear in the case of *engrailed* (*en*). Although the effect of *engrailed* mutants is predominantly in the posterior compartments (Morata & Lawrence 1975; Lawrence & Morata 1976) there are sometimes morphological anomalies in the anterior compartment of the wing that might suggest a requirement of en^{+} in the anterior compartment. Also, *engrailed* lethal alleles show a fusion of embryonic segments which affects anterior regions (Kornberg 1981; Nüsslein-Volhard & Wieschaus 1980). However, mosaic analyses (Morata & Lawrence 1975; Lawrence & Morata 1976; Lawrence & Struhl 1982; Morata *et al.* 1983) indicated that the requirement for *engrailed* is exclusively restricted to the posterior compartments; the effect sometimes seen in the anterior compartment is a secondary consequence of the abnormal development of the posterior one. This has been recently confirmed when molecular probes of the expression of *engrailed* have been used (Kornberg *et al.* 1985).

In some cases the homeotic mutants are zygotic lethal and only by means of this type of analysis is it possible to study their homeotic effect on the adult structures. This is the case of the lethal mutations of the bithorax complex such as *Ubx* (Morata & Kerridge 1981; Kerridge & Morata 1982) *abd-A* and *Abd-B* (Sánchez-Herrero *et al.* 1985), *Polycomb* (Struhl 1981*b*) and *Antennapedia* revertants (Struhl 1981*a*).

One important result arising from these and other experiments is that the realms of action of homeotic genes often coincide with compartment boundaries, suggesting that compartments are the anatomical units of homeotic gene function. For example, the genes *Ubx* and *abd-A* (Sánchez-Herrero *et al.* 1985) are both defined by anteroposterior compartment boundaries, in the second thoracic segment for *Ubx* and in the first abdominal segment for *abd-A*.

The structure and pattern of spatial expression of the *Ubx* gene has been studied in more detail (Morata & Kerridge 1981; Kerridge & Morata 1982; Casanova *et al.* 1985). Its function

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is principally required in four compartments: T2p, T3a, T3p and A1a (T for a thoracic segment, A for abdominal, a for anterior, p for posterior compartment). Correspondingly, the gene contains four distinct functions called *postprothorax* (*ppx*), *bithorax* (*bx*), *postbithorax* (*pbx*) and *bithoraxoid* (*bxd*) specific to each one of the four compartments (Casanova *et al.* 1985). The elimination by mitotic recombination of Ubx^+ activity in clones of cells illustrate the developmental independence of these four functions. For example ppx^+ acts only in early development; in its absence compartments T2p and T3p develop as T1p. However, when Ubx^+ is eliminated after 8 h of development (Morata & Kerridge 1981) there is no effect on T2p and no prothoracic transformation at T3p, indicating that ppx^+ is already dispensable. By contrast, clones of this time produce a mesothoracic transformation at T3a and T3p. Furthermore, there are individual mutations within the *Ubx* gene which inactivate one but not the other functions of Ubx^+ (Casanova *et al.* 1985).

The functional interactions between different homeotic genes have been studied by Struhl (1982), producing clones of cells made mutant simultaneously for two or three homeotic genes. The results strongly suggest that homeotic genes act in a combinatorial manner, the development of a given polyclone being determined by the particular combination of active homeotic genes. These experiments also suggest that the presence (or absence) of one homeotic gene may affect the expression of others. Particularly relevant is the observation made by Struhl (1982) that the *ppx* phenotype of Ubx^- clones is suppressed by the absence of Scr^+ thus suggesting that one of the roles of Ubx^+ is to prevent the inappropriate expression of Scr^+ in T2p and T3p compartments.

Production of marked clones in mutant flies

Many of the homeotic mutants are viable and a cell lineage analysis of mutant flies can be performed. In those cases in which the transformation is complete or nearly so, for example the mutation bx^3 transforming T3a into T2a, the proliferation parameters of the mutant disc are altered to mimic those of the disc on which it is transformed (Morata & García-Bellido 1976). More interesting are the mutations showing partial transformation like *Antennapedia*, *engrailed* (García-Bellido & Santamaría 1972), *Contrabithorax* (Morata 1975) and bx^1 (Sánchez-Herrero & Morata 1983). In these cases the mutant disc presents a mixture of cells differentiating wildtype or mutant structures, where one can investigate the lineage of the two sets of structures. This is a pertinent experiment because as the precursors of the different discs develop apart since the embryonic period, one would expect the mixed mutant patterns to arise from differential determination (for either mutant or wildtype structures) in early development. This would imply a separate lineage for each type of structure. In the bithorax phenocopies, induced by ether treatment around the blastoderm stage, it has been reported that there is a lineage segregation for normal and mutant structures (Capdevila & García-Bellido 1977).

However, in the mutations studied in detail like $Antp^R$ (Postlethwait & Schneiderman 1969, 1971), Cbx^1 (Morata 1975), en^1 (García-Bellido & Santamaría 1972) and bx^1 (Sánchez-Herrero & Morata 1983) the observed result is that marked clones can extend to both mutant and wildtype territories, clearly establishing that there is no differential lineage for the two types of structures; the progenitor cell of a clone generated in the third larval period of these mutant discs, for example in the wing disc of Cbx^1 or in the haltere disc of bx^1, may have some of the progeny differentiating haltere and the others wing structures. There is no stability in the state of determination of mutant cells (figure 3, plate 2).

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A plausible interpretation for these results is based in the concept that the state of determination depends on the amount of product of the responsible gene in a cell autonomous way. This idea is strongly suggested by the experiments described in the preceding section that demonstrate that individual cells alter their specific state of determination if they are depleted of the corresponding gene function. Thus the maintenance of the normal determination depends on a continuous supply of gene product. In the case of mutants producing partial transformation there is probably still some gene function left, so that some cells have enough wildtype product to acquire a normal determination while others have not. The level of gene product would depend on local growth conditions, proliferation rate and so on. In these mutants the final differentiation of cells will be conditioned in a trivial manner by these factors. The experiments indicate that due to the lack of an appropriate amount of gene product the state of determination of the cells is unstable and emphasize the critical role of homeotic genes in establishing and maintaining normal determination.

The cell lineage of *Antennapedia* (*Antp*) has been used to determine the effect that the position of the primordia of the imaginal disc has on the homeotic genes *engrailed* and *Ultrabithorax* (Morata & Kerridge 1982). In flies carrying the mutation $Antp^{73b}$ the antenna develops into a leg that is often virtually identical to the normal mesothoracic leg (figure 4, plate 3). Thus, these flies have two sets of mesothoracic legs, one in normal position and another in the place of the antennae. In this latter structure it has been shown that the anteroposterior compartment boundary is established at around 72 h of development (Morata & Lawrence 1979) unlike the other appendages where it is established at blastoderm or shortly afterwards (Steiner 1976; Lawrence & Morata 1977). As the existence of an anteroposterior boundary requires the expression of the gene *engrailed* (Morata & Lawrence 1975; Lawrence & Morata 1976), the time of establishing of the boundary can be taken as indicative of en^+ function. When blastoderm clones are generated in $Antp^{73b}$ flies, those in the thoracic legs respected the anteroposterior compartment boundary, whereas those in the antennal leg did not define any lineage restriction at that time. Only when produced after 72 h did they define the anteroposterior boundary, exactly as the normal antenna. This experiment indicates that the main factor in the expression of the *engrailed* gene is the position of the primordia and not the type of appendage they eventually form. It also suggests that the same gene can be independently activated at different times in different organs.

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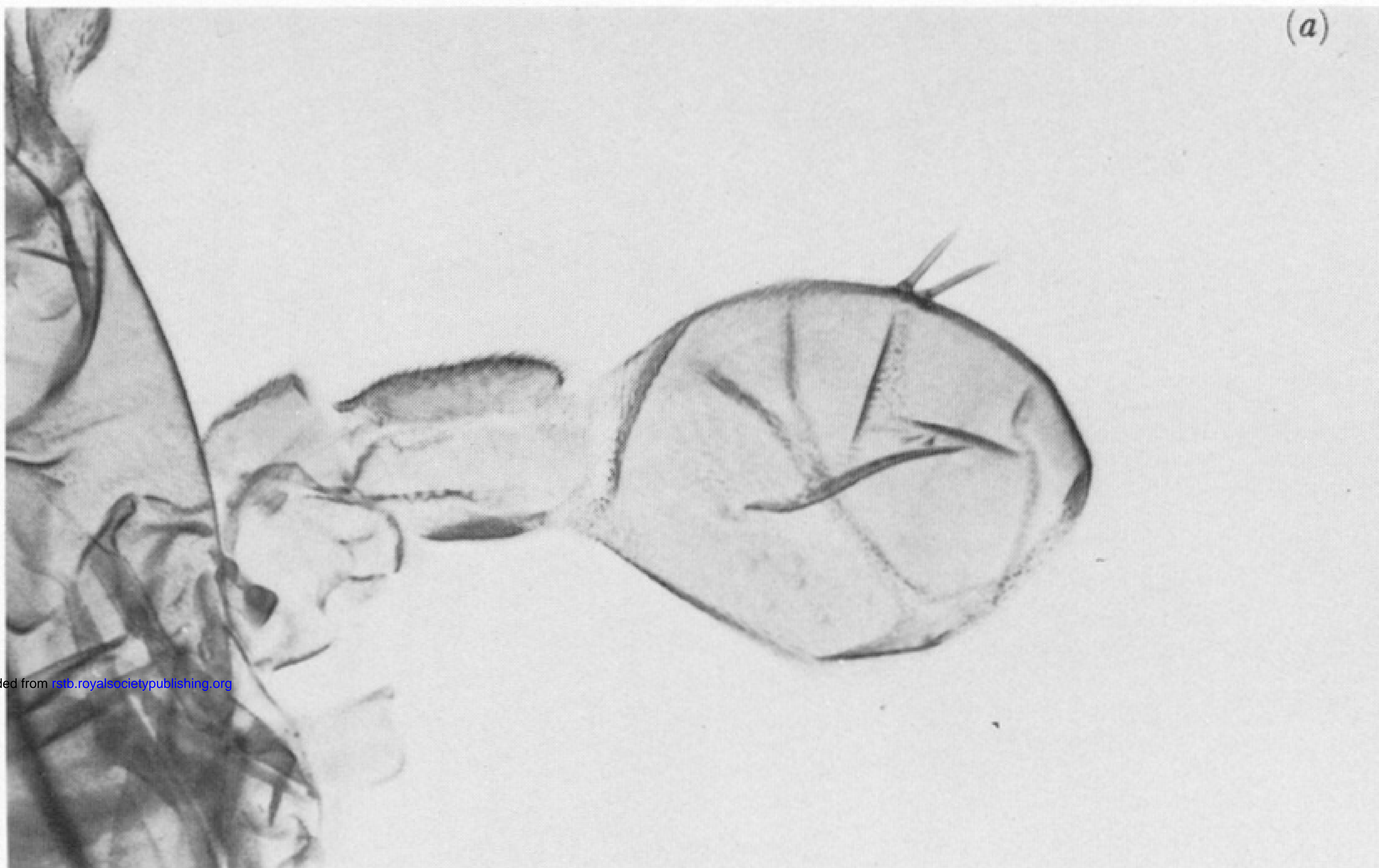

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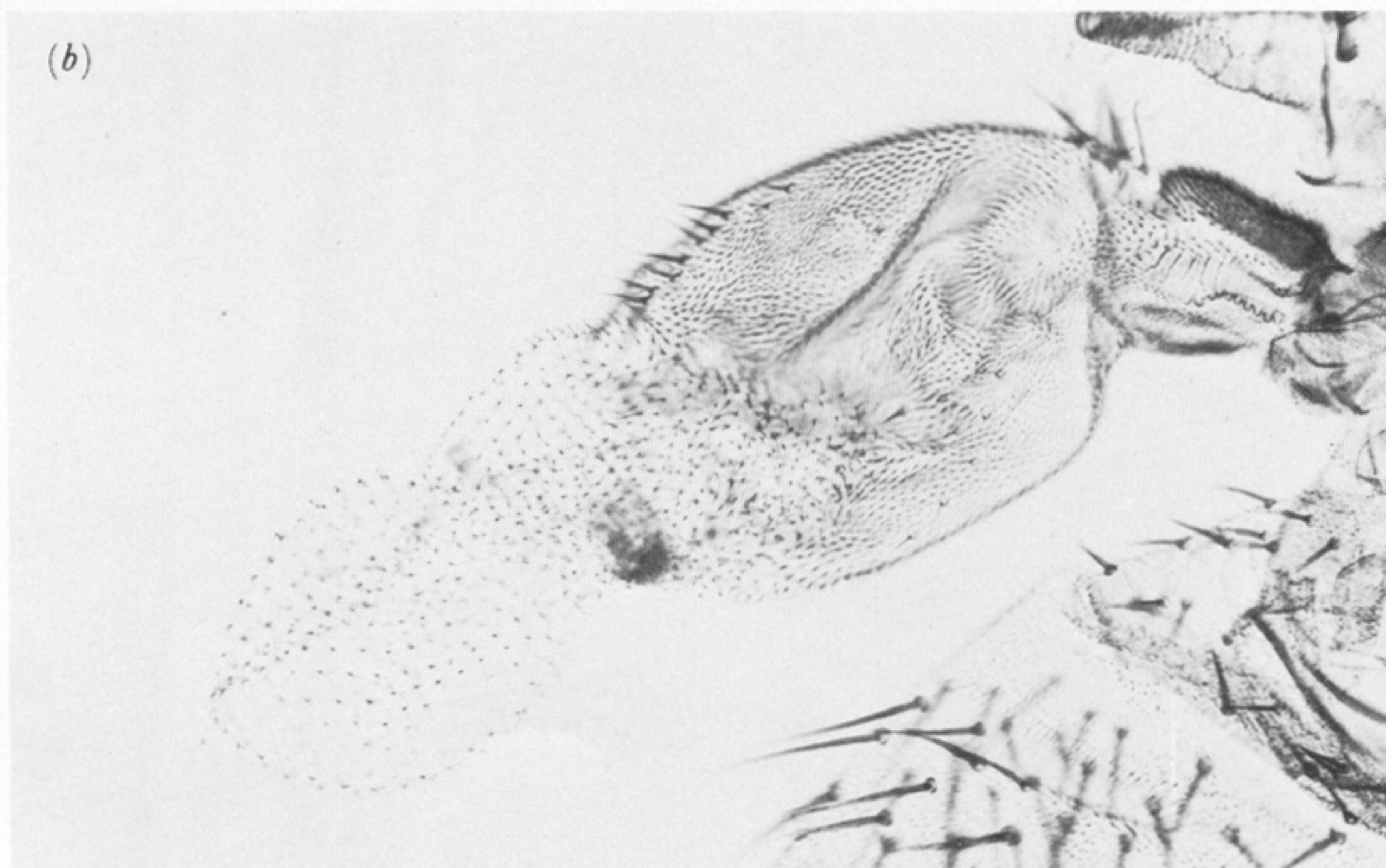

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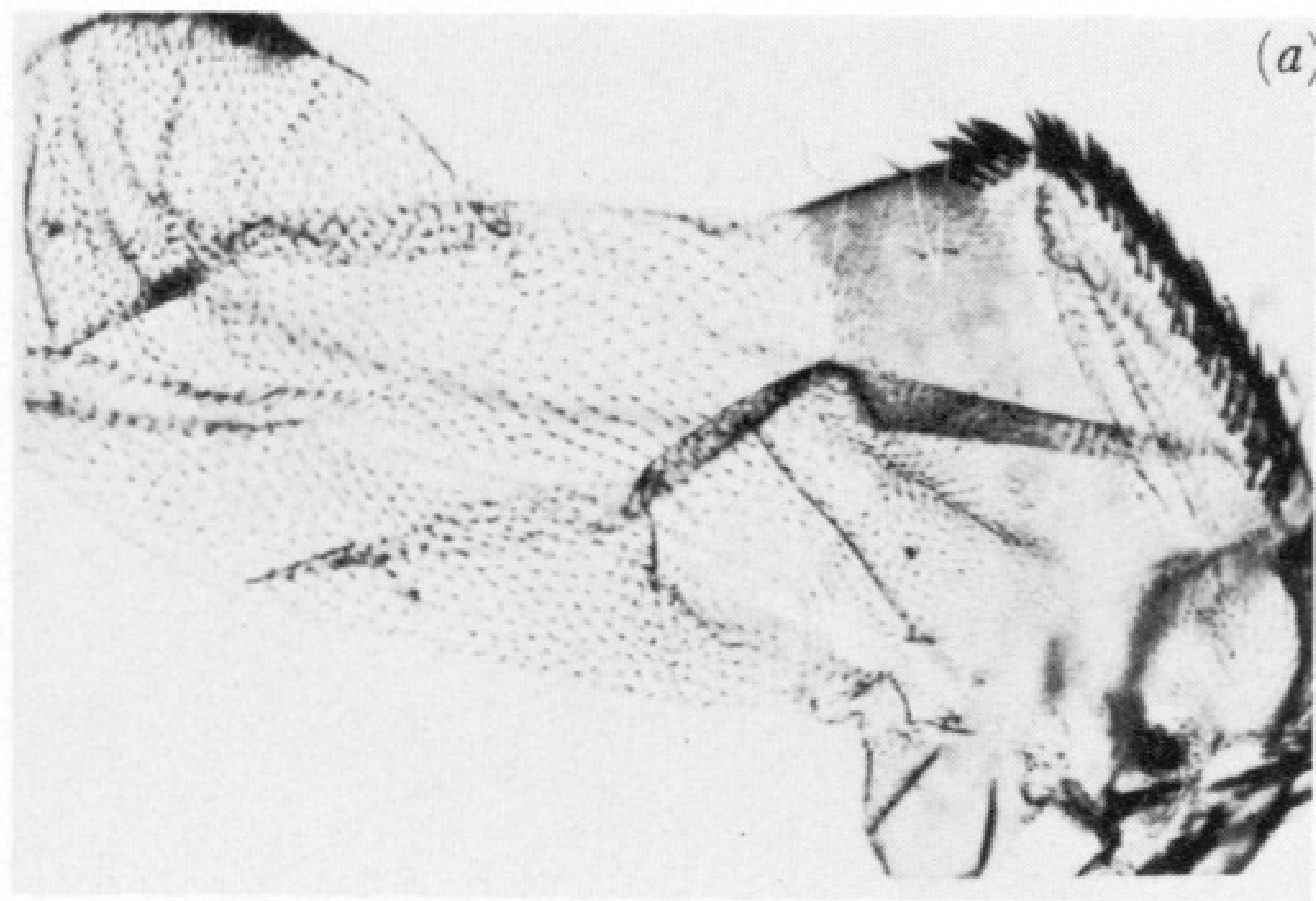
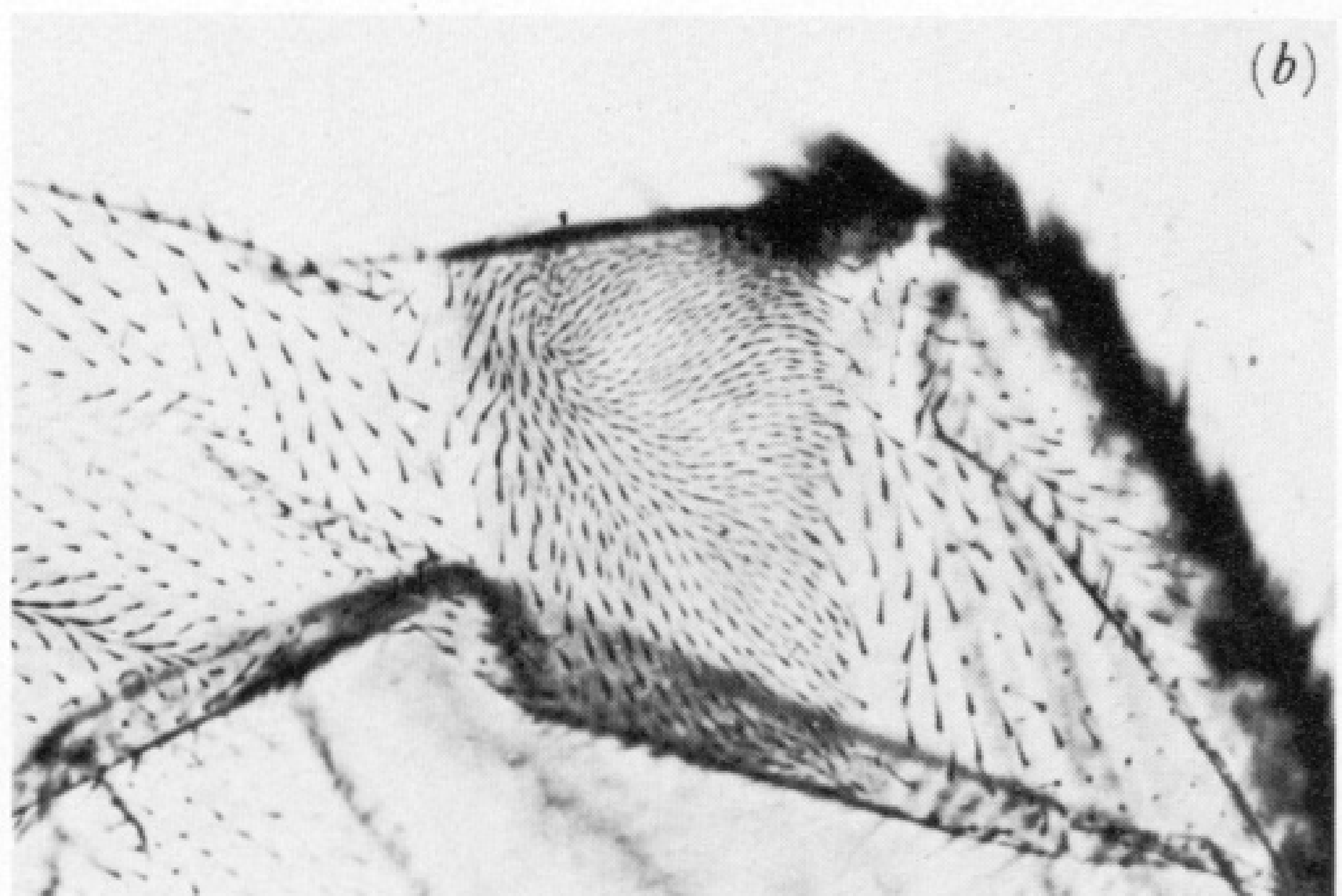
FIGURE 2. Cell autonomy of homeotic genes. a) small bx^3 homozygous clone in the haltere generated in the third larval period. It consists of two bristles typical of the anterior margin of the wing. The cells show the mutant phenotype surrounded by wildtype haltere cells. b) a larger Ubx^- clone showing differentiation of typical wing trichomes in the haltere.





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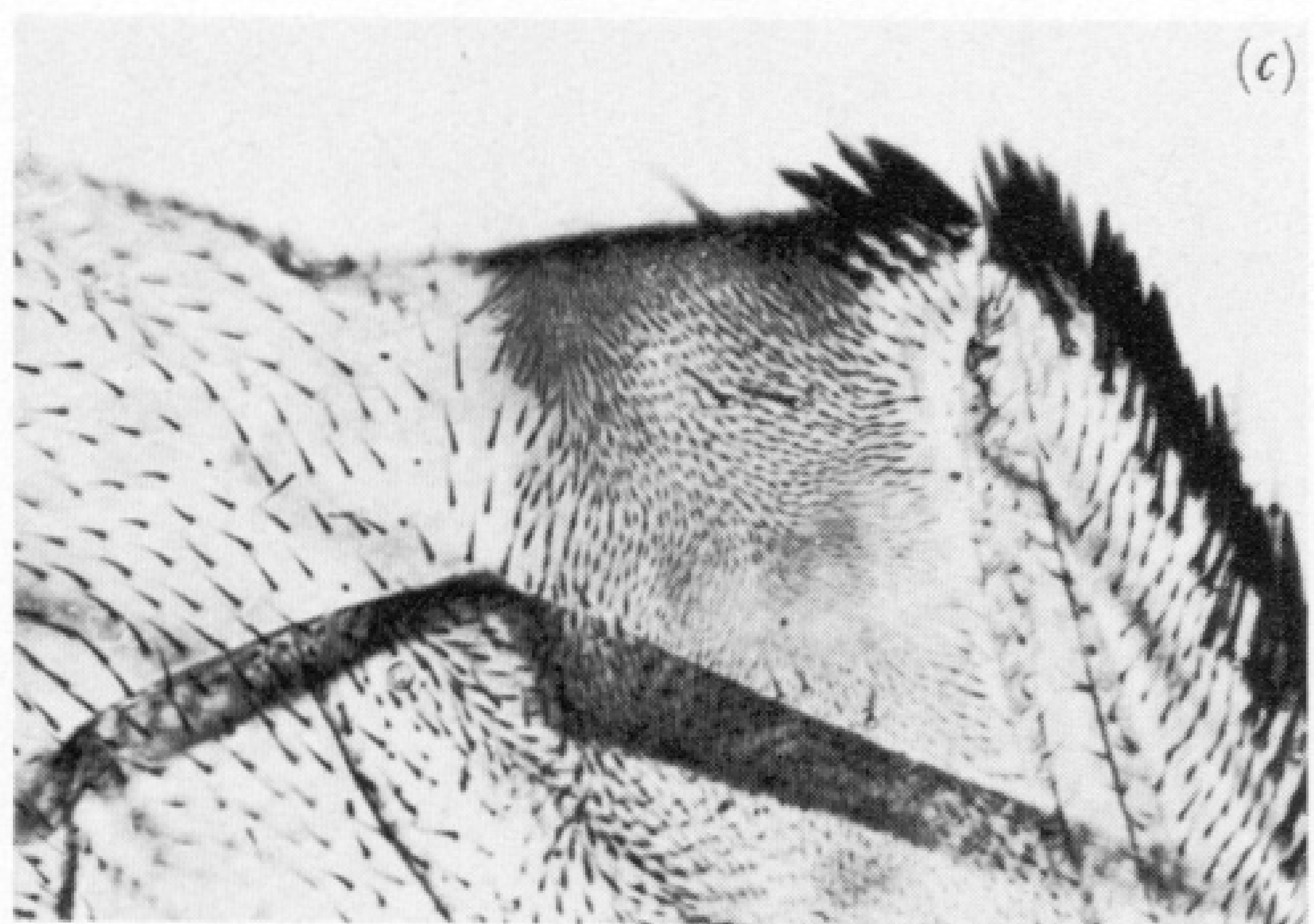

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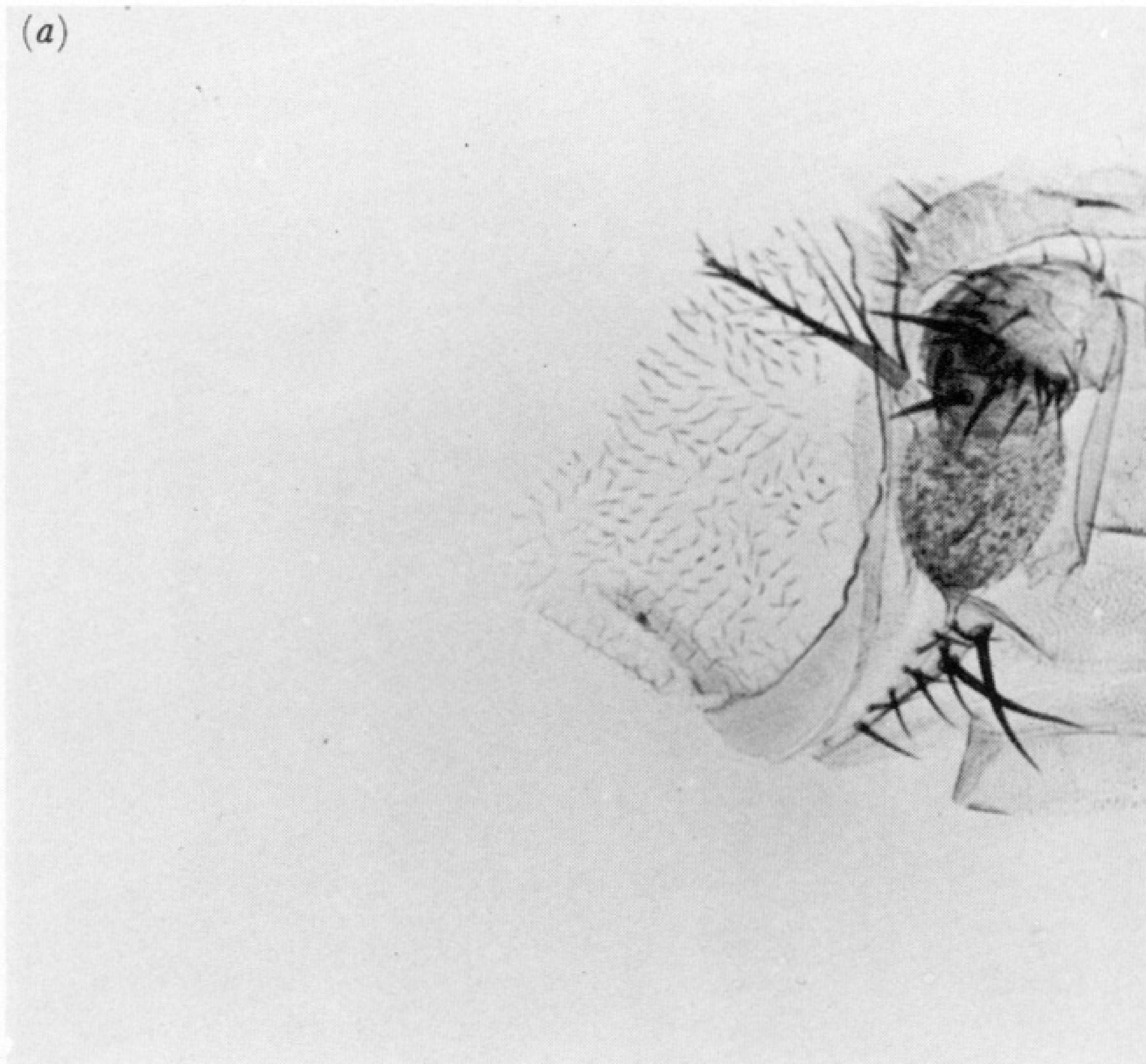
FIGURE 3. A typical Cbx^1 homozygous wing appendage. (*a*) Entire appendage, (*b*) and (*c*) dorsal and ventral views of the same structure. Notice the sharp distinction between haltere and wing territories. In this case the line separating wing and haltere runs in almost exactly homologous positions in the dorsal and ventral areas. Clones generated in a mosaic appendage like this can extend to both wing and haltere territories even if initiated late in larval development (Morata 1975).



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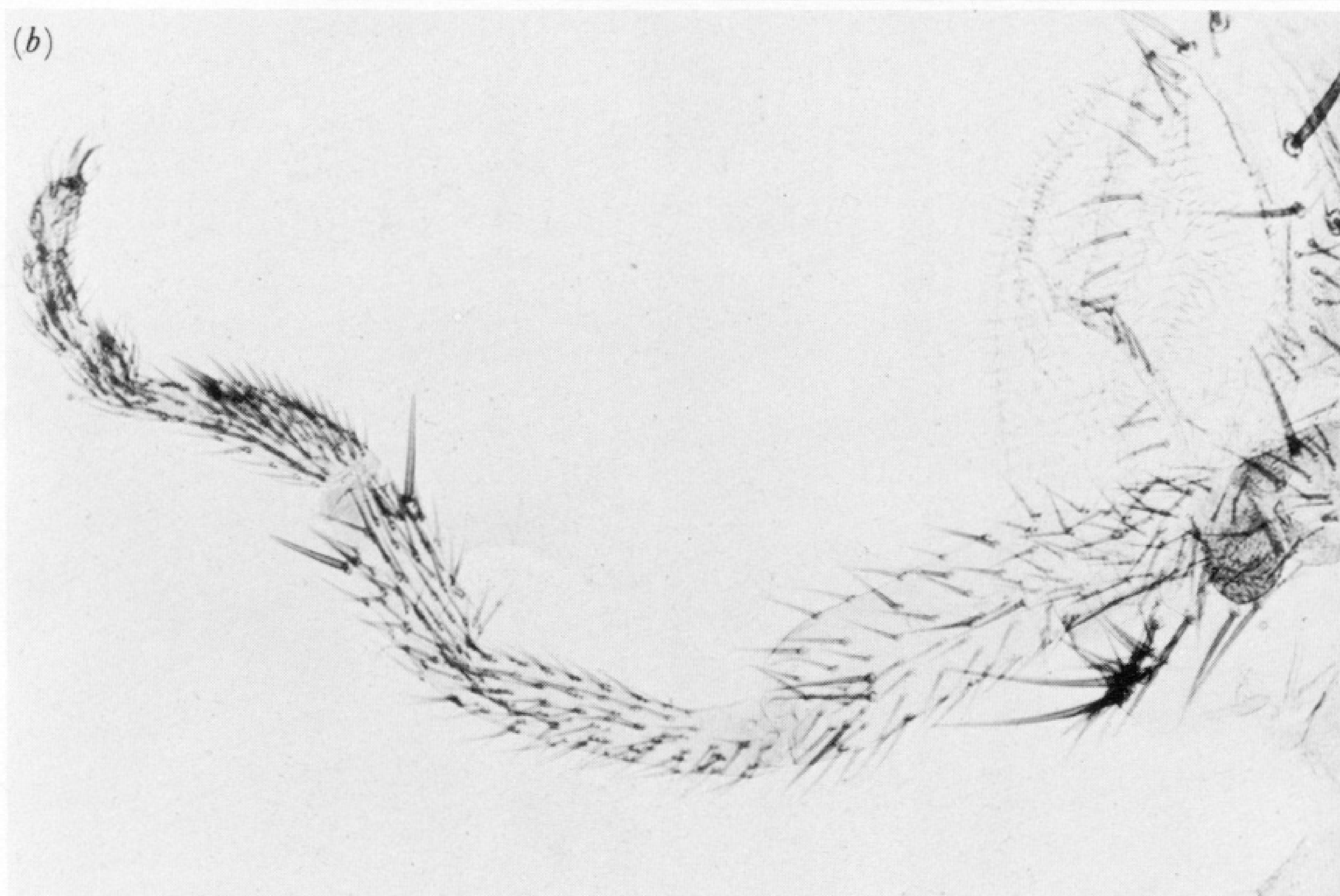

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FIGURE 4. Head of an *Antp*[73] fly (*b*) showing the transformation of an antenna into a leg of mesothoracic type. A normal antenna is shown for comparison (*a*). In spite of the obvious morphological differences between the two appendages the time of establishing of the anteroposterior boundary is the same. By contrast, in the normal mesothoracic leg the anteroposterior boundary is established much earlier (Morata & Kerridge 1982, see text).