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The cellular dynamics of pattern formation in the eye of *Drosophila*

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SUMMARY

The establishment and early development of the ommatidial bundles in the presumptive eye of *Drosophila* have been investigated using electron microscopic serial sectioning. A progression of developmental stages has been characterized. Initially simple, symmetrically constructed bundles develop into asymmetrical, more complex constructions. Computer graphic reconstruction has been used to show the three-dimensional structure of the various ommatidial bundles. Autoradiography has been used to locate the position of a region of cell division which is intimately associated with the formation of the ommatidial bundles.

INTRODUCTION

The insect compound eye, in which cells are arranged in a crystal-like lattice, has been the subject of many developmental studies (see Shelton, 1976), and the development of the Dipteran eye has been well characterized (see Meinertzhagen, 1973), particularly in *Drosophila* (Waddington & Perry, 1960; Ready, Hanson & Benzer, 1976; Campos-Ortega, 1980). In *Drosophila*, the ommatidia (the sub-units which collectively form the compound eye) are made up from only a few cell types arranged in a precise spatial manner (Ready *et al*. 1976), and from the third larval instar, during which time incipient retinal assembly becomes apparent, onward, certain of these cell types can be identified and their subsequent development followed (Ready *et al*. 1976).

The study of pattern changes that occur as development proceeds can help in understanding the mechanisms which direct cellular interaction and differentiation within a developing system. The developing eye of *Drosophila*, in which individual pattern elements can be identified and their spatial rearrangements followed, lends itself well to such study. Using serial section electron microscopy the establishment and progression of pattern within the developing eye tissue were followed during a short developmental period. From an initially simple, symmetrical pattern, a complex asymmetrical one develops. Integral to the breaking of the symmetry and progression towards complexity appears to be the greater expression of individual cell identity.

Key words: *Drosophila*, pattern formation, symmetry, electron microscope, compound eyes.

MATERIALS AND METHODS

Drosophila melanogaster of the Massachusetts strain were reared at 25 °C, under the usual conditions.

Fixation

Cephalic complexes were dissected from larvae, fixed for half an hour in a cooled mixture of 1 % glutaraldehyde and 1 % osmium tetroxide (0·1 M-phosphate buffer, pH 7·2), and then post fixed for two hours in cooled 2 % osmium tetroxide (phosphate buffer). The tissue was dehydrated in alcohol and then left overnight in an equal mixture of propylene oxide and Durcupan resin (Polaron Equipment Limited, Hertfordshire, U.K.). The head discs were then teased free from the cephalic complexes and polymerized in resin.

Sectioning

Sections were cut on a Reichert-Jung Ultracut using an Emscope 3 mm diamond knife. Progressive ribbons of five sections were picked up onto Formvar-coated Gilder GS 2×1 slot grids, and stained with Reynolds' lead citrate (Reynolds, 1963). Sections were examined using a Phillips 301 electron microscope.

Autoradiography

Following Ready *et al.* (1976), third instar larvae were injected with 0·1–0·5 µl sterile aqueous 48 Ci mmol^{-1} [^{3}H]thymidine. Cephalic complexes were dissected from treated larvae and processed as previously described. 1 µm sections were dried onto gelatinized slides. The slides were dipped in Ilford K5 emulsion (Ilford, Essex, U.K.) diluted by half with distilled water, dried and sealed in silica gel desiccated boxes stored at 4 °C. The emulsion was developed in ID19 and fixed in 25 % sodium thiosulphate, and the tissue was stained with toluidine blue.

Three-dimensional reconstruction using computer graphics

The system of programs used to reconstruct the ommatidial bundles were all kindly supplied by Robert Ransom.

The outlines of relevant cells from each section were first transferred to tracing paper and a Tektronix 4663 Plotter/Digitizer was used to input the data into a DEC VAX 11/780 computer. Twenty-four points per cell were digitized, each point being recorded as the X and Y displacements from a central fixed origin.

Using an 80×80 intiger array, the cellular outlines could be displayed, for each cell the vectors between each pair of sequentially digitized points being interpolated. The image of the stacked sections could then be viewed. A hidden lines program routine prevented those parts of the ommatidial bundle that should be obscured from view when observed from any particular position, from being drawn. A program feature allowing any number of cells to be removed provided a means of 'dissecting' the reconstructed bundles to reveal constituent elements.

THE STRUCTURE OF THE ADULT OMMATIDIUM

Within the ommatidium two distinct parts can be recognized – the lens, or dioptric system, which gathers and channels the light, and the underlying photo-sensitive tissue, the retina. The dioptric system consists of an external cornea which overlies a fluid-filled lumen, the pseudocone; this being bordered at its sides by pigment cells and basally by the four cone cells (Fig. 1). The photosensitive region contains a central core of eight receptor cells (R cells) which is ensheathed by pigment cells. Each receptor cell carries a light-sensitive rod, or rhabdomere, and the eight receptor cells are so arranged that at any depth within the retina only

seven rhabdomeres can be observed (Fig. 1). The rhabdomeres of six of the receptor cells (R1–6) are arranged in an asymmetrical trapezoid pattern, and extend the depth of the retina. The rhabdomere of R7 is found central to this trapezoid in the distal regions of the retina, and that of R8 is the central rhabdomere in the proximal regions. About the rhabdomeric pattern the R cells are positioned radially, the rhabdomeres of R7 and R8 being held on projections which 'squeeze' through between R1 and R6, and R1 and R2 respectively (Fig. 1).

THIRD INSTAR EYE DEVELOPMENT

Eye differentiation begins in *Drosophila* during the third larval instar (Waddington & Perry, 1960), and the major steps in this process have been elucidated by Ready *et al.* (1976), from which the following is largely derived. The prospective eye tissue is first proliferated by general cell division which appears as an anteriorly moving broad band of activity. Following this is the anterior sweep of a dorsoventral constriction in the tissue, the morphogenetic furrow (MF) (Fig. 2). The MF marks the front of an anteriorly extending area of tissue patterning which
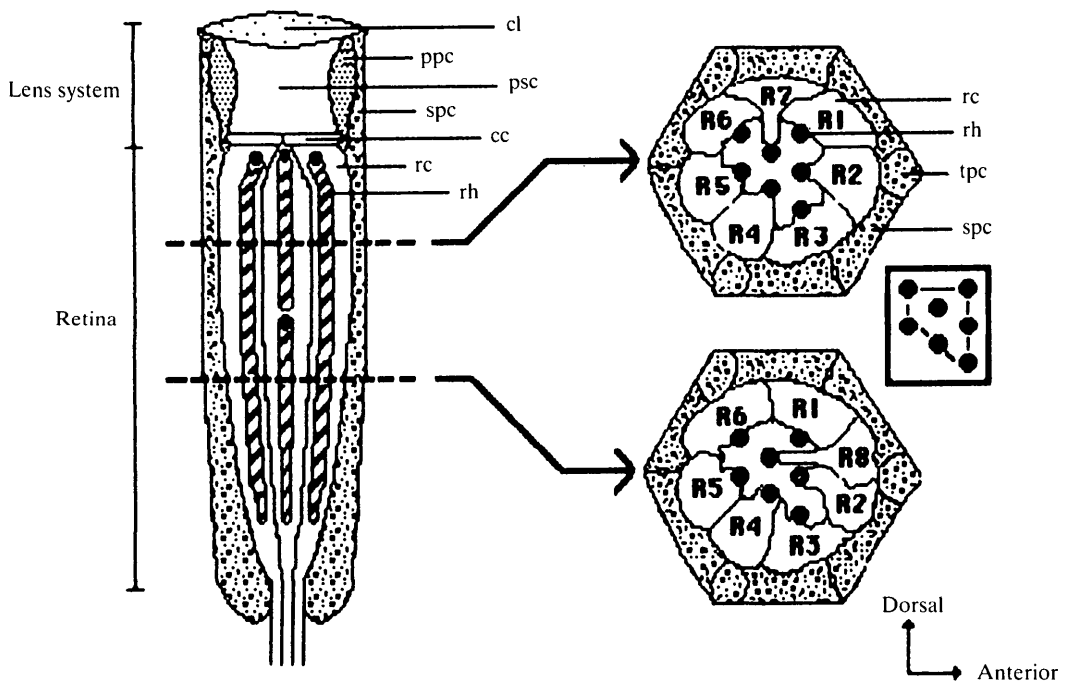

Fig. 1. Diagram displaying the construction of the adult ommatidial unit. The rhabdomeric pattern found in both inner and outer parts of the retina is shown in the inset box. The rhabdomeres of R1–6 form an asymmetrical trapezoid shape around the central rhabdomere. Note how the rhabdomere of R8 is the central rhabdomere deeper in the tissue, whereas R7 performs this role higher up. cc: cone cell; cl: corneal lens; ppc: primary pigment cells; psc: pseudocone; rc: receptor cell; rh: rhabdomere; spc: secondary pigment cell; tpc: tertiary pigment cell.

reaches the anterior margin of the eye tissue about 10 h after pupation (Campos-Ortega & Hofbauer, 1977). Intimately associated with the pattern formation is a second set of cell divisions, which appears as a tight band to the posterior of the MF (Fig. 2). Only the cells destined to form R2, R3, R4, R5, and R8, are not involved in this second band of mitotic activity – they have already passed through their terminal divisions. These five cells bundle to produce a structure termed the precluster, to which is added three more receptor cells (R1, R6, and R7), derived from the second band of division, to produce ommatidial bundles containing the adult complement of eight receptor cells.

The larval eye tissue is contained within the head imaginal disc, the anlagen which gives rise to an eye, an antenna, and some head cuticle. This is an ectodermal invagination of a single layer of cells that comprises a thick columnar epithelium separated from the thinner peripodial membrane by a fluid-filled lumen (Fig. 2). The eye tissue of the third larval instar is found in the posterior portion of the thick columnar epithelium (Fig. 2), and throughout the instar persists as a pseudostratified monolayer epithelium, all cells, with the exception of those undergoing division, extend the apical/basal depth of the epithelium. The movements that occur within this tissue relate essentially to the nuclei of the various cells. The pseudostratification results from the differential positioning of the nuclei.

Because the development of the eye displays an anteroposterior temporal spread, the more posterior a region of tissue is from the anteriorly advancing MF, the more developed it is. By progressively moving posteriorly from the MF, increasingly developed tissue is encountered, and it is in this manner that the tissue development was investigated.

Running centrally in an anteroposterior direction across the adult eye is the equator, which is defined by the ommatidial pattern inversion which occurs about it. The equator divides the eye into dorsal and ventral halves, and the patterning of the ommatidia in one half is the mirror image of the other (Dietrich, 1909). This equator is established in the patterning of the eye tissue during the third larval instar (Ready et al. 1976). To aid simple description of the patterning, only data taken from ventral right eye tissue will be presented. The development occurs in
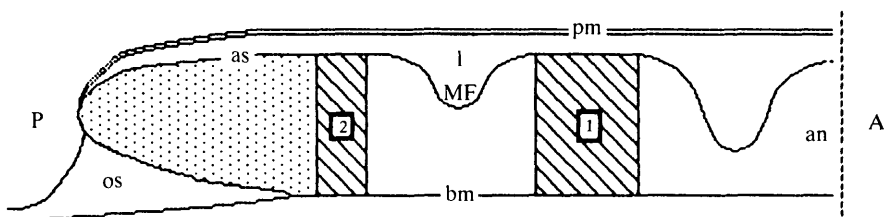

Fig. 2. Diagram of longitudinal section through the eye region of the third larval instar head disc. The two bands of cell division are indicated by hatching, and the speckled area is the region of the eight-cell clusters. A: anterior; an: antennal part of disc; as: apical surface; bm: basement membrane; l: lumen; MF: morphogenetic furrow; os: optic stalk; P: posterior; pm: peripodial membrane.
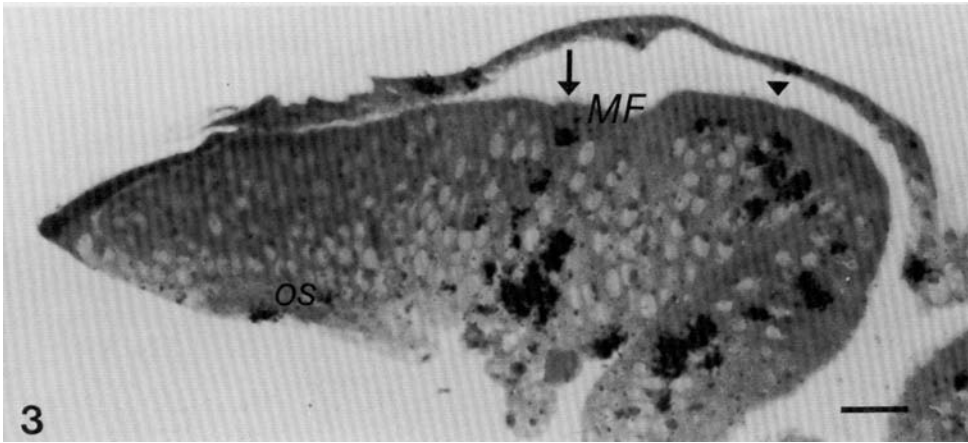
Fig. 3. Autoradiograph of longitudinal section of disc fixed 4 h after labelling *in vivo* with [³H]thymidine. Anterior is to the right. Arrow: second band of labelling; Arrowhead: proliferative band; *MF*: morphogenetic furrow; *os*: optic stalk. Bar = 20 µm.

the dorsal part in exactly the same manner, the ommatidial bundles are just orientated in the opposite direction.

RESULTS

The location of the second band of cell division

The electron microscopic investigation indicated the second band of division and the precluster to be closely associated with the MF (Fig. 4). The position of the second band of division has hitherto been indicated to be further posterior than this (Ready *et al*. 1976). An autoradiographical study was undertaken to clear this up. Prior to division a presumptive retinal cell detaches from the basement membrane, rounds up in the apical region of the tissue, division follows, and 'feet' are then extended back to the basement membrane (Ready *et al*. 1976). From the electron microscopic investigations to be presented here, it is known that all postmitotic nuclei from the second band of division move to the basal regions. Hence, when this division is studied autoradiographically, the label ([³H] thymidine taken up by the cells during premitotic DNA synthesis) in the apical regions of the tissue most accurately indicates the division's anteroposterior position. Fig. 3 shows an autoradiograph of a longitudinal section through the disc, and the label of the second band of division in the apical regions can be seen closely associated with the MF.

The production of the eight-cell ommatidial bundles

In the centre of the MF all nuclei are confined to the basal regions, and as the mitotic cells rise to the apical surface to divide, the postmitotic nuclei of R2, R3,

R4, R5, and R8 begin a migration to the apical regions and the structured precluster becomes evident. Fig. 4A shows an apical section through the region of the second band of division. R2, R3, R4, R5, and R8, the cells not involved in this division, are bundled into the characteristic precluster shape and cell division, evident as cytokinesis, is locally occurring. All postmitotic nuclei from the second band of division move back to the basal regions, so in the tissue just posterior to the zone of cell division the epithelium has the nuclei arranged in two layers; an apical layer of the nuclei of the cells R2, R3, R4, R5, and R8, and a basal layer containing the nuclei of all the other cells (R1, R6, R7, cone cells, pigment cells, and others). Present within this tissue the newly formed eight-cell clusters can clearly be seen, and their nuclei segregated into the two levels; R2, R3, R4, R5, and R8 are found apically and R1, R6, and R7 basally (Figs 5, 6).

From the tissue arrangement just described, the adult eye develops. As has already been described, the adult ommatidial unit has a precise construction, and interestingly, these early bundles do not initially show the expected cellular rearrangements towards that construction, rather, they first move to establish a highly symmetrical clustering arrangement.

The establishment of the symmetrical cluster

Within the early eight-cell bundles R8 occupies the central position, and, particularly within the apical regions, each of the other receptor cells occupies a specific position about its border (Fig. 5). The nuclei of R6, R1, and R7, in that sequence, begin to rise from the basal layer towards the apical surface as the other receptor cell nuclei rearrange in the apical level (Fig. 6). Once the nuclei of R6 and R1 are incorporated into the apical region (R7 does not complete its migration until well after this has happened), the clustering becomes symmetrical about a centrally positioned line passing between R3 and R4, and bisecting R8 and R7 (Fig. 7B). The symmetry of this clustering reveals itself in the paired appearance of R1 and R6, R2 and R5, and R3 and R4, about R8, which can be clearly seen in the computer graphic reconstructions of the cluster (Fig. 8). The pairing is a manifestation of the fact that the behaviour of one member of a pair on the anterior side of the cluster is identical to that of the other member on the posterior side. Thus, at this stage, the six cells destined to form the outer rhabdomeres (R1–6), appear to be of only three types – R(1/6), R(2/5), R(3/4). Indeed, without knowledge of which is the anterior side of the cluster it is impossible to distinguish the two members of a pair. It is not implied that in all aspects the two cells of a pair are at this stage identical, the fact that one is on the anterior, and the other the posterior side of the cluster in itself negates this. Rather, the members of a pair are seen as responding identically to the cues directing the dynamics of the cluster. The extent to which the cells of a pair are sharing common identity will be discussed later.

All eight of the receptor cells within this cluster project developing axons. These group as an axonal bundle and pass through the deeper regions of the tissue, where
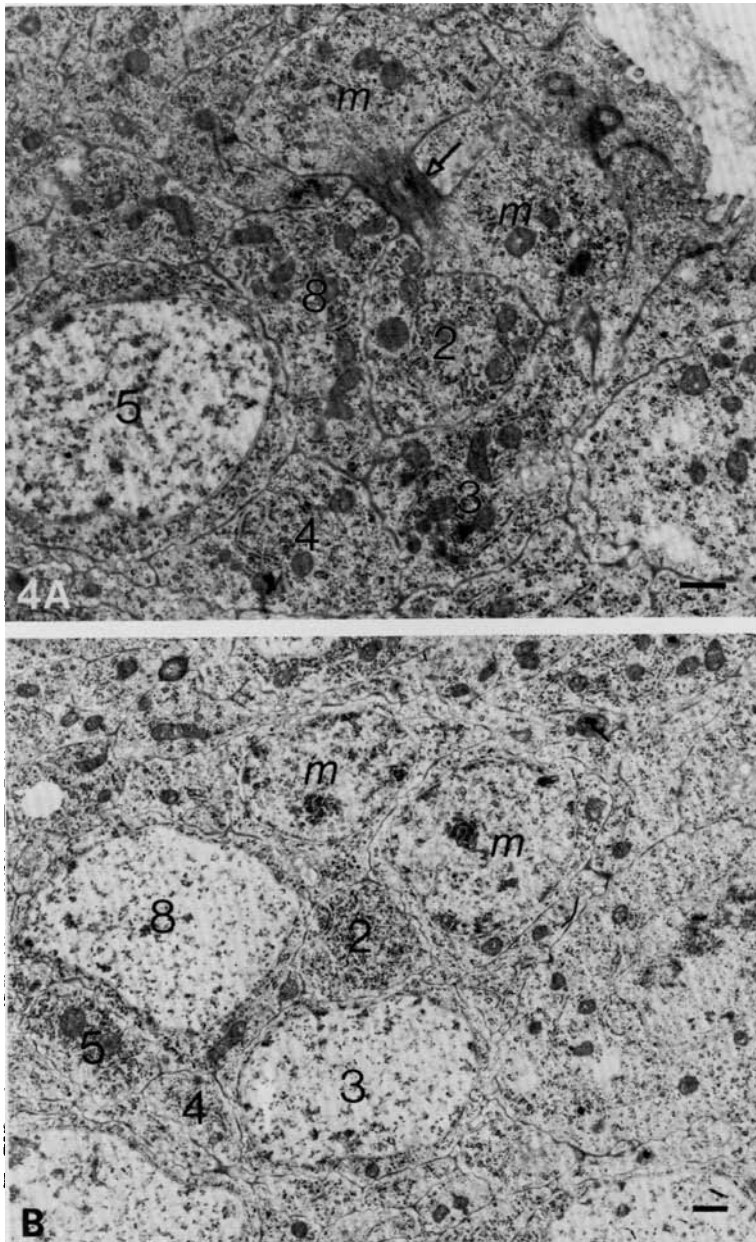
Fig. 4. Sections through tissue in the very posterior of the morphogenetic furrow. The cells of the precluster are numbered. Bars = 0·5 µm. Anterior is to the right. (A) Close to the apical surface. A constriction furrow (arrow) is separating a dividing cell into daughters (*m*). (B) 30 µm below apical surface. The two newly formed daughter nuclei (*m*) from division apparent in (A) are on their migration back to the basal regions.
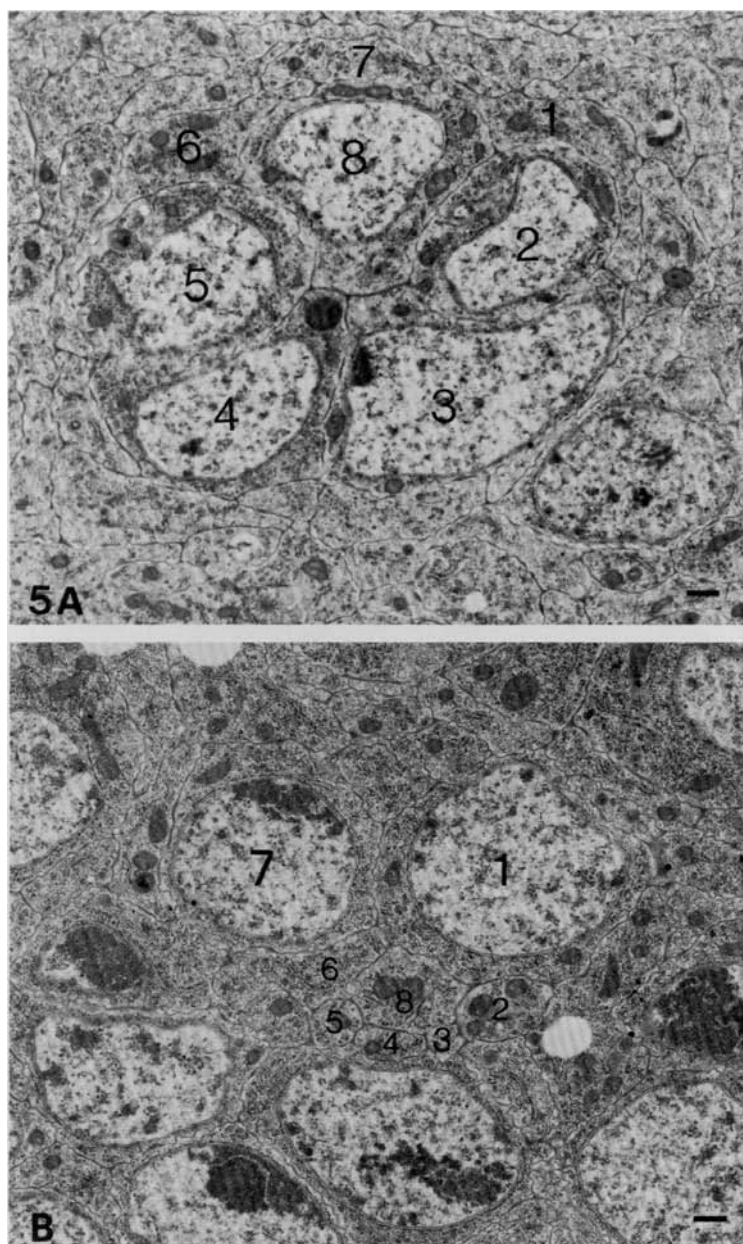
Fig. 5. Sections through an early eight-cell bundle. All receptor cells are numbered. Bars = 0·5 μm. Anterior is to the right. (A) 7 μm below apical surface. The nuclei of R2, R3, R4, R5, and R8 are located in the apical regions of the tissue. Note the symmetrical appearance of the bundle in this apical section. (B) 30 μm below apical surface. The nuclei of R1 and R7 can be seen in the deeper regions along with the non-receptor cell nuclei. R6 nucleus is found somewhat higher than these two.

now only non-receptor cell nuclei are found (Fig. 7C). Entering the optic stalk, they turn posteriorly and pass backwards, under the more mature tissue, *en route* to the brain. The axonal bundle is constructed in a similar manner to the symmetrical cluster. The axons of R1–7 are arranged sequentially about the central constituent R8. This structural arrangement persists through to the adult eye (Ready *et al.* 1976).

This symmetrical cluster is established some three to four rows behind the newly formed eight-cell clusters, which is equivalent to 6 to 8h of development (the second band of division advances one ommatidial row per 2h (Campos-Ortega & Hofbauer (1977)). In the adult eye the dioptric system overlies the retina, only the rhabdomeric part of R8 is found central to the receptor cell clustering, and the other receptor cells are arranged in an asymmetrical manner. So, during the first 6 to 8h of their development the eight-cell bundles show little movement towards an adult constitution; the nuclei of the lens-secreting cone cells are still in the basal parts of the tissue, R8 persists in occupying a central position, and the clustering as a whole is displaying remarkable symmetry.

Once the symmetrical cluster has been established then adult characteristics begin to follow.

The two-cone-cell stage

As the R7 nucleus completes its migration into the apical region, two cone cell nuclei rise from the basal region and come to flank the receptor cell clustering, one to the anterior and the other to the posterior (Fig. 9). Because three more nuclei are now included with those grouped in the symmetrical stage, a different packing arrangement is now adopted. In the symmetrical stage the cells which show paired appearance (R1 and R6, R2 and R5, R3, and R4) are arranged about the central cell at three levels, but now a two-tier system is adopted (Fig. 11). The nuclei of R3, R4, and R7 are the closest to the apical surface, and the projections to the apical surface from the underlying R1, R2, R5, R6, and R8 form a characteristic 'bow-tie' shape (Fig. 9).

Examination of the computer graphic reconstructions of this cluster (Fig. 10) reveals, that although the clustering pattern has changed, the cell pairing appears to persist, *i.e.* the symmetry of the cluster seems preserved. However, close scrutiny of Fig. 9 shows R4 to be displaced slightly from contact with R8. This only occurs in the most apical few microns of the tissue, at all other depths R4 is found in contact with R8 and pairing with R3, but in the strictest sense it must be said that the cluster is no longer symmetrical. The two-cone-cell stage is found approximately two rows to the posterior of the symmetrical stage and indications of the adult characteristics to follow are present; two cone cell nuclei are present in the apical region, and the expected breakdown of the symmetry is indicated by the slight displacement of R4 from contact with R8 – this being the initiation of the considerable displacement which becomes manifest in the following four-cone-cell stage.

The four-cone-cell stage

Rising from the basal region, the two other cone cell nuclei now come to lie in the apical regions. The nuclei of R3, R4, and R7 withdraw back into the tissue (Fig. 11), leaving the four cone cells to surround the apical projections of the receptor cells (Fig. 12A). The symmetry of the earlier clusters is now lost. This is clearly illustrated by the positioning of R4 within the cluster. In the most apical regions, the projection of R4 is completely separated from its bundled seven counterparts (Fig. 12A), slightly deeper down it contacts the receptor cell bundle but not R8, and to gain its correct position within the axonal bundle (between R3 and R5, and contacting R8 – see above), it skirts the extremity of R5 (Fig. 13).

The characteristic central position of R8 in the earlier clusters is now being lost. The nucleus of R8 is pushing out anteriorly between R1 and R2 (its location in the adult eye) (Fig. 12B), the line of symmetry does not persist and the cluster shows a generally different construction (Fig. 13). Concomitant with the breakdown of the symmetry is the breakdown of the cell pairings, and thus, R1, R2, R3, R4, R5, and R6 are now all individually distinct pattern elements.

This four-cone-cell stage is the most advanced cellular arrangement achieved by the eye tissue before pupation, and obvious adult characteristics have now been acquired. The lens-secreting cone cells now occupy the apical regions of the tissue and overlie the prospective photosensitive receptor cells. The earlier symmetry
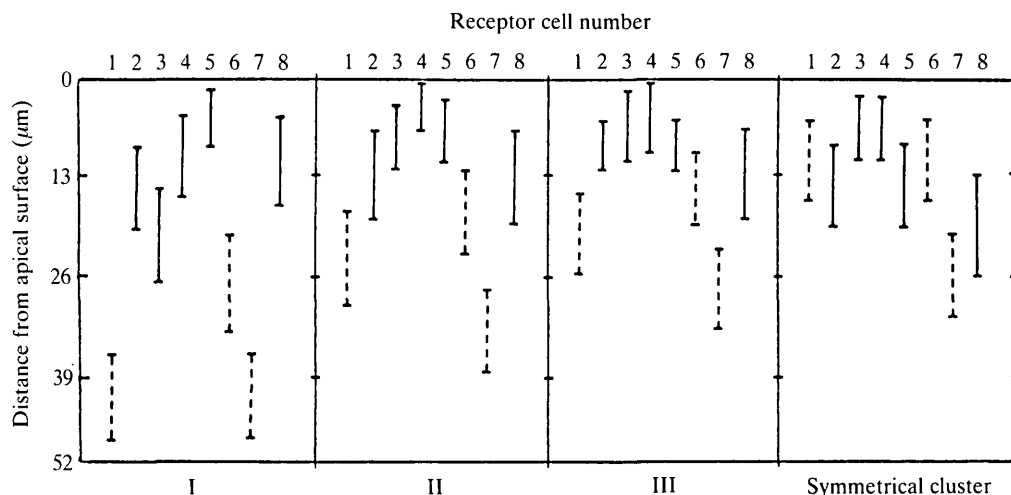

Fig. 6. The positioning of the receptor cell nuclei found in four sequentially placed ommatidial bundles leading directly from a newly formed cluster (I) to the symmetrical cluster. The nuclei of R1, R6, and R7 (dotted) are initially found in the basal regions and progressively rise over the next few ommatidial rows.

Fig. 7. Sections through a symmetrical cluster. All receptor cells are numbered. Bars = 0·5 μm. Anterior is to the right. (A) 5 μm below apical surface. Note that non-receptor cell nuclei are still not present in the apical regions. (B) 8 μm below apical surface. Note how the clustering is symmetrical about the centrally positioned line. (C) 35 μm below apical surface. The bundle of eight axons passing through the deeper regions where the non-receptor cell nuclei are located.
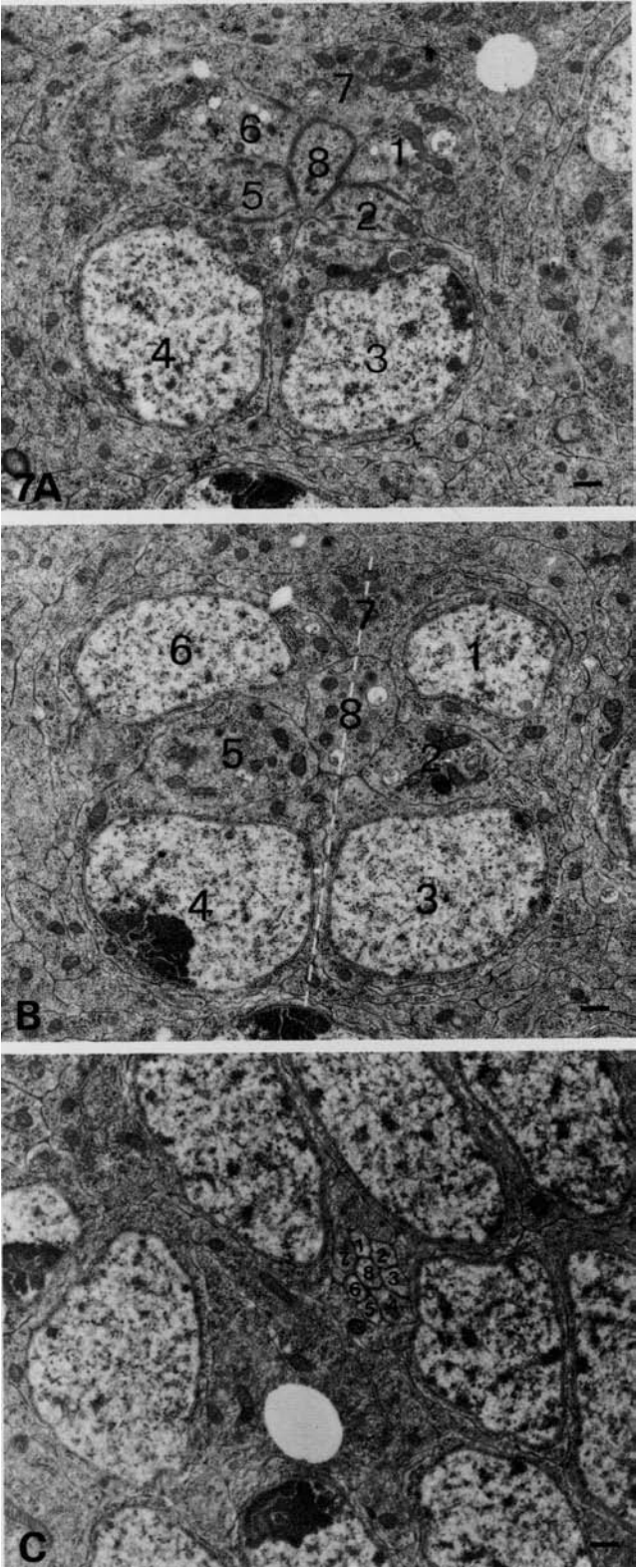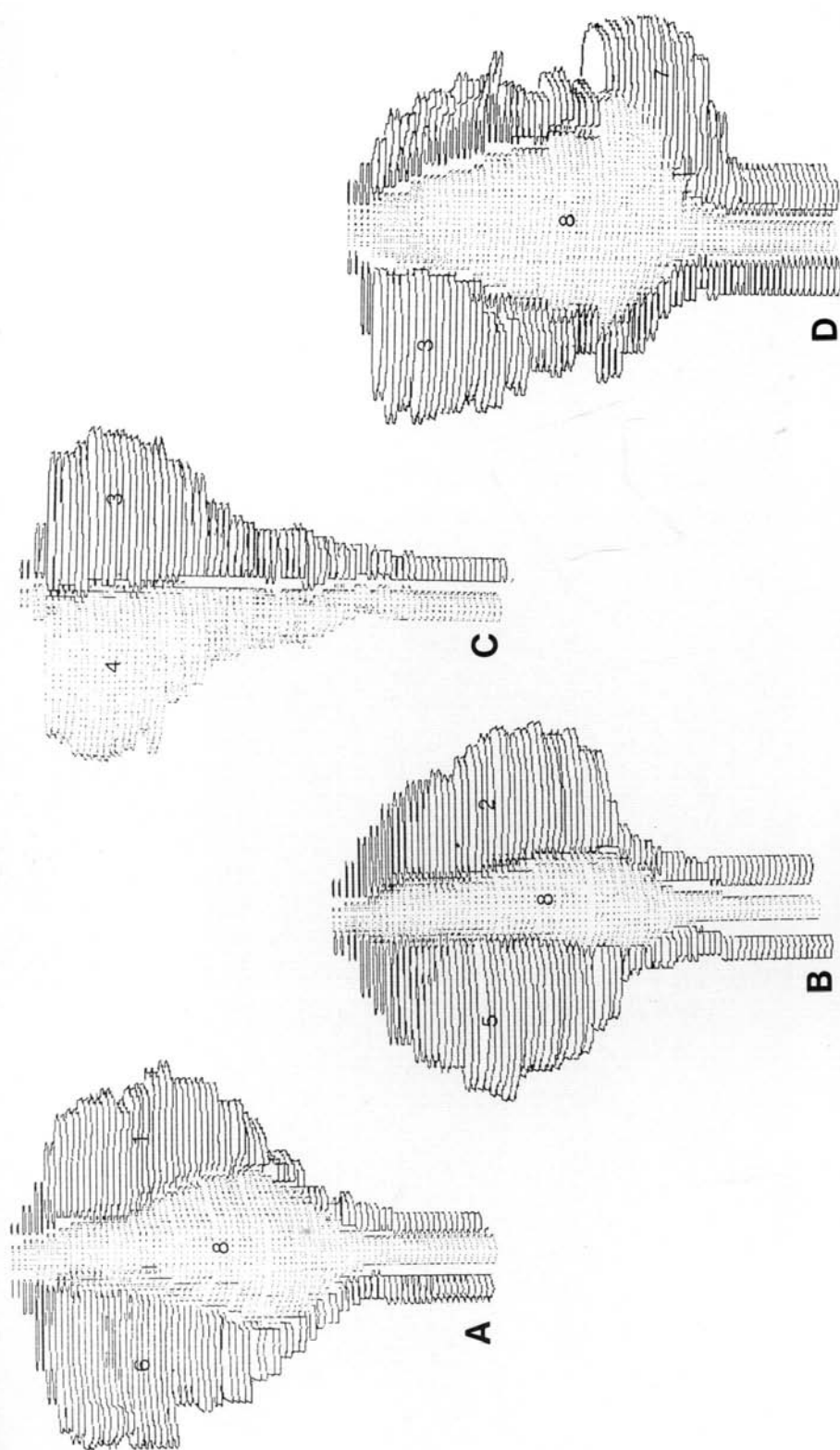
Fig. 8. Computer graphic reconstructions of the receptor cells of the symmetrical cluster. All receptor cells are numbered. Note how R1 and R6, R2 and R5, and R3 and R4 show paired appearance (A,B,C – all viewed from a ventral position, *i.e.* standing behind R3 and R4). The nucleus of R7 can be seen to be relatively basally positioned (D – viewed from an anterior position).

has been lost, all eight of the receptor cells are displaying individual characteristics, and R4 and R8, in particular, are showing the type of morphological movements required to produce the asymmetrical pattern found in the receptor cells of the adult eye.

DISCUSSION

There exists a wide variety of evidence that within the eight receptor cells the three subgroups, R1–6, R7, and R8, exist. R1–6 provide the outer rhabdomeres, R7, in the outer part of the eye, and R8 in the inner, provide the central rhabdomere. Three types of photosensitive pigment are found in the retina; R1–6 contain one type, and R7 and R8 each carry a different type (Harris, Stark & Walker, 1976). The mutation *outer rhabdomeres absent* produces, as the name implies, a phenotype in which the outer rhabdomeres (those of R1–6) are not formed, and the mutation *retinal degeneration B* produces a similar condition in which the outer rhabdomeres degenerate in later life (see Harris *et al.* 1976). The mutation *sevenless* produces an eye in which R7 is absent, R1–6 being unaffected (Campos-Ortega, Jurgens & Hofbauer, 1979; Harris *et al.* 1976). In neurological
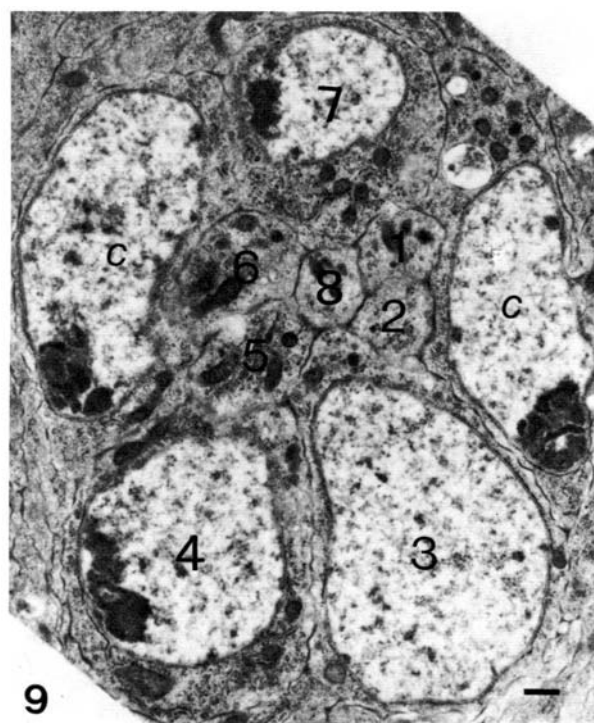

Fig. 9. Section through a two-cone-cell cluster, 5 μm below apical surface. All receptor cells are numbered. Two cone cell nuclei (*c*) are now present in the apical regions. They lie anterior and posterior to the 'bow-tie' arrangement of the apical projections of R1, R2, R5, R6, and R8. Anterior is to the right. Bar = 0·5 μm.
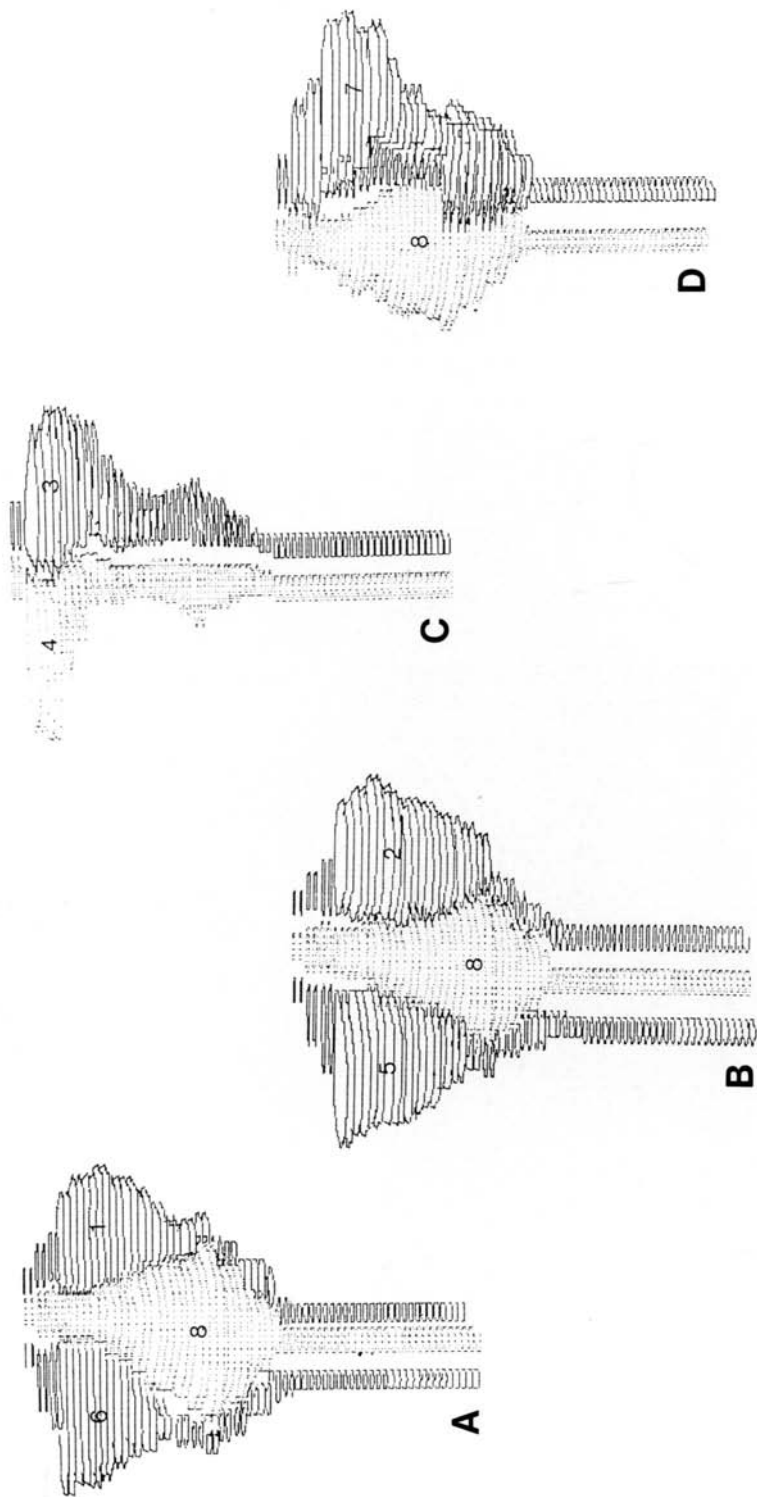
Fig. 10. Computer graphic reconstructions of the receptor cells of the two-cone-cell cluster. All receptor cells are numbered. Note how R1 and R6, R2 and R5, and R3 and R4 still show paired appearance (A,B,C – all viewed from a ventral position). The nucleus of R7 has now joined the apical clustering (D – viewed from an anterior position).
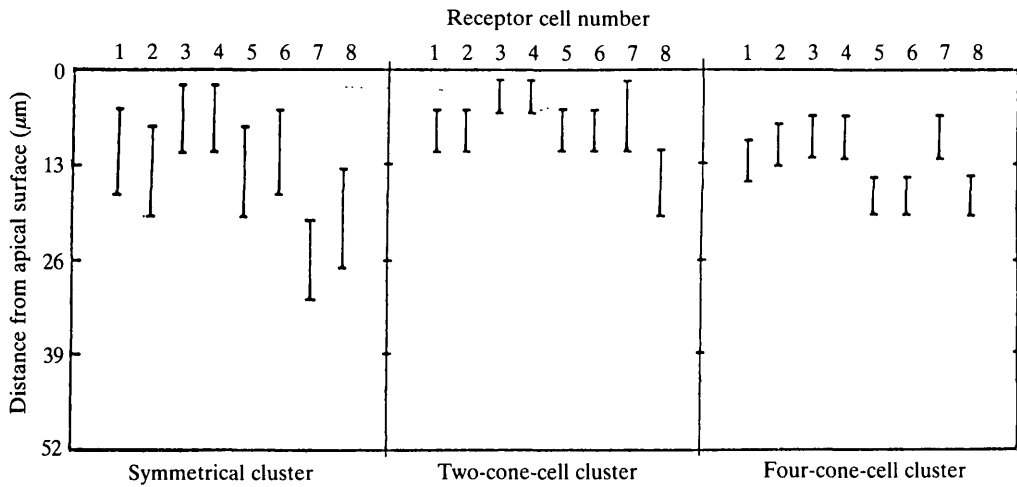
Receptor cell number

Fig. 11. The positioning of the receptor cell nuclei in the symmetrical, two-cone cell, and four-cone-cell clusters.

terms, R1–6 bear short axons which terminate in the lamina ganglion (Meinertz-hagen, 1975), and R7 and R8 project long axons which synapse at different levels in the medulla ganglion (Campos-Ortega *et al.* 1979). The eight cells of the symmetrical cluster can be distinguished into exactly the same subgroups; there is the central cell (R8), the six which pair about the line of symmetry (R1–6) and the remaining cell (R7). Being recognizable elements of the symmetrical cluster, the subgroups have thus acquired distinguishing identity by this stage and it is likely that they are fundamental pattern elements. That is to say, the eight receptor cells are not initially determined to general receptor cell development before individual, or subgroup, identity is acquired. If this was the case then the earliest bundles should not be structured. Unstructured bundles do not occur. In the newly formed bundles progressing towards the symmetrical cluster stage, the future bilateral symmetry of the bundle as a whole is evident in the apical regions (Fig. 5A), and hence, as structural elements, the subgroups are established. It is the rearrangement that occurs within the apical/basal axis (Fig. 6) that leads to the formation of the fully symmetrical cluster.

It is possible that the formation of the symmetrical clusters is an expression of simple adhesive differences between the constituents of the incipient eight-cell bundles. Far greater credibility is given to this proposal when it is coupled with the evidence that the ommatidial units undergo 'self-assembly'. When third instar eye development in *Drosophila* is disrupted for a short period, by any of a number of procedures (Becker, 1957; Poodry, Hall & Suzuki, 1973; Foster & Suzuki, 1970; van Breugel, Vermet-Rozeboom & Gloor, 1975), a corresponding dorsoventral scar appears in the adult eye. The position of the scar is found more anteriorly when induced in older larvae and its anterior advance with age corresponds closely with the advance exhibited by the second band of division (Campos-Ortega &

Hofbauer, 1977). Because the second band of division is known to be closely associated with the laying down of the pattern, then it can be inferred that it is this
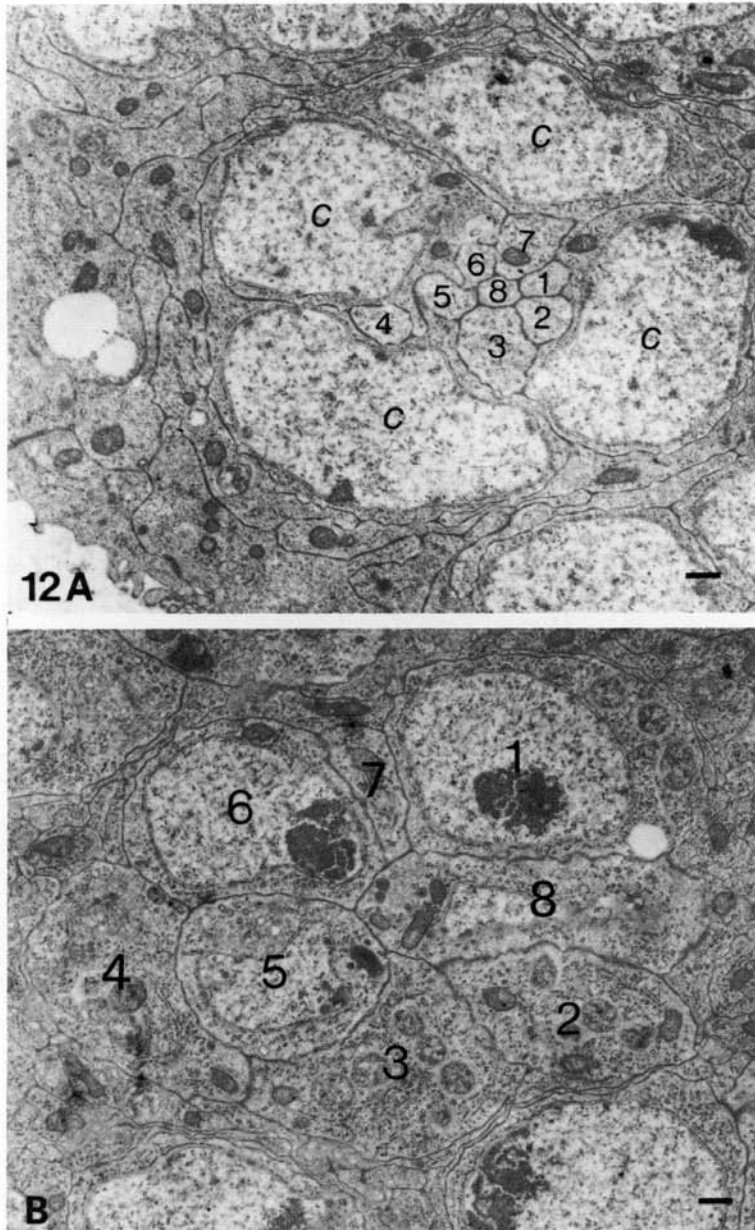

Fig. 12. Sections through a four-cone-cell cluster. All receptor cells are numbered. Bars = 0·5 μm. Anterior is to the right. (A) 5 μm below apical surface. The apical projections of the receptor cells are surrounded by the four cone cell nuclei (c). Note the displacement of R4. (B) 15 μm below apical surface. Note how R8 is pushing out between R1 and R2, and how R4 does not contact R8.
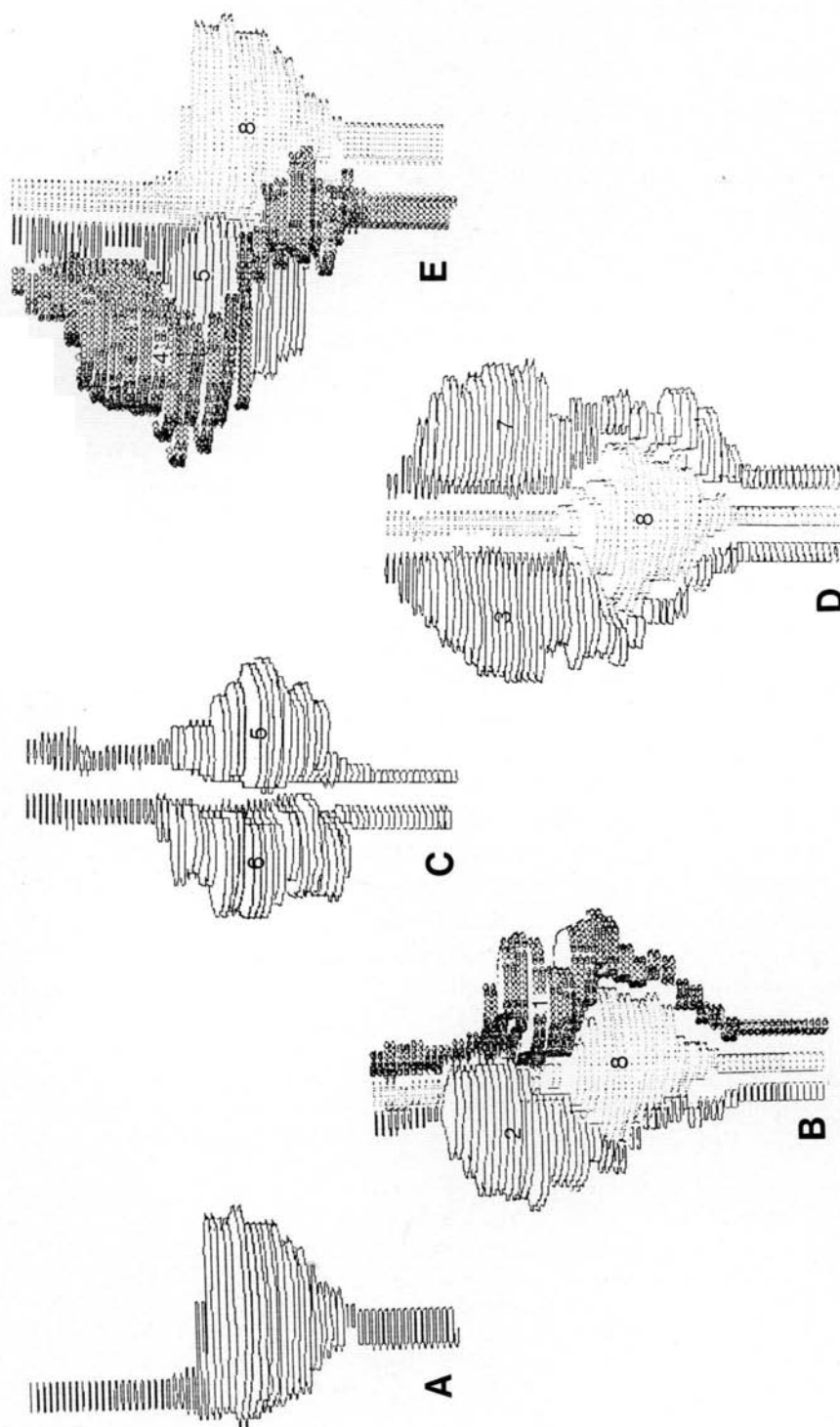
Fig. 13. Computer graphic reconstructions of the receptor cells of the four-cone-cell cluster. (A) The appearance of R8. Note the anterior bulge resulting from this cell pushing out of the cluster. Viewed from a ventral position, anterior is to the right. (B) R8 pushing out between R1 and R2. Viewed from an anterior position. (C) R5 and R6 viewed from the posterior. (D) R3 and R7 viewed from the anterior. (E) R4 skirts R5 to come to occupy its correct axonal position. Viewed from a ventral position, anterior is to the right.

developmental region that is the target of the scar-inducing treatments. Since the tissue anterior to the scar is correctly patterned, then the growing crystal model (Ready *et al*. 1976) now seems unlikely. In this model, where cells are recruited onto a growing lattice front, once the front is disrupted then pattern aberration should then extend to the anterior margin of the eye. Lebovitz & Ready (in preparation) have now cogently demonstrated the ability of eye disc fragments to pattern autonomously, the previously established pattern to the posterior not being required.

Symmetry and self-assembly are often closely associated with simplicity of construction. This has been shown with the tobacco mosaic virus (Fraenkel-Conrat & Williams, 1955), the T4 bacteriophage (Wood & Edgar, 1967), the flagella of *Salmonella* bacteria (Abram & Koffler, 1964), and microtubules (Weisenburg, 1972), amongst many other examples. Although the system being dealt with here is on a much more macroscopic scale than the examples cited, the symmetry and the 'self-assembly' of the ommatidial bundles may similarly be indicating that the initial patterning is established using 'simple' rules. That is to say, the eight receptor cells form a symmetrical pattern because they cluster under the direction of only a limited variety of simple adhesive interactions. The members of a pair of cells within the symmetrical clusters are viewed as identical in terms of their adhesive interactions. Take for example the pair R1 and R6. These two cells not only adopt the same shape and appearance (mirror image inversion accepted) but also have identical cellular contacts – each contacts R8, R7, and R(2/5). The breaking of the symmetry and the loss of identical adhesive interactions shown by members of a pair go hand in hand. Once the symmetry is broken then erstwhile members of a pair display individual, idiosyncratic, adhesive interactions. The move from symmetry to asymmetry is viewed as mirroring the change from simplicity to complexity. As time proceeds, then differentiation can occur, and more complex adhesive interactions can result, and the simplicity, the symmetry, gives way to the complexity required to construct the asymmetrical patterns. The later movement towards construction of asymmetry may thus be viewed as cellular differentiation building upon the simply constructed foundation pattern.

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