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# A spatial relationship between innervation and the early differentiation of vibrissa follicles in the embryonic mouse

R. J. VAN EXAN* AND M. H. HARDY

*Department of Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada N1G 2W2*

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## INTRODUCTION

The vibrissa (sinus hair) follicles of rodents, unlike most of the abundant pelage follicles, are well developed tactile sense organs (Melaragno & Montagna, 1953; Montagna & Ellis, 1958; Winkelmann, 1959) which are concerned with locomotion guidance and equilibration (Vincent, 1912; Park, 1970).

As sense organs, the vibrissa follicles are intricately associated with the central nervous system. The follicles of the adult are well innervated, in their connective tissue capsules and outer root sheaths, with sensory nerve endings of the maxillary branch of the trigeminal nerve (Tello, 1905, 1923; Vincent, 1913; Weddell & Pallie, 1954; Montagna & Ellis, 1958; Winkelmann, 1959). Each vibrissa is represented in the somatosensory cortex of the mouse by a distinct neuronal aggregation termed a 'cortical barrel' (Woolsey & Van der Loos, 1970). Correspondence has been established between the arrangement of the sinus hairs and that of the cortical barrels in mice (Van der Loos & Woolsey, 1973; Lee & Woolsey, 1975; Woolsey & Wann, 1976; Killackey, Belford, Ryugo & Ryugo, 1976) and in rats (Welker, 1971, 1976; Waite, 1973; Killackey *et al.* 1976; Axelrad, Verley & Farkas, 1976). The precise agreement of cortical barrels and vibrissa follicles with respect to number, array and function suggests some form of communication between elements of the central nervous system and the vibrissa follicles during the development of the sensory system.

The major mystacial vibrissae of the mouse and rat are arranged on the snout in five 'horizontal' (rostrocaudal) rows and one 'vertical' (dorsoventral) row which lies just caudal to the horizontal rows (Fig. 1). There is no variation in the location of the vibrissa follicles in the mouse, and their numbers in the major groups are remarkably constant (Danforth, 1925; Grüneberg, 1943*a*; Dun, 1958; Yamakado & Yohro, 1979), except in a few mutants (Jacobson, 1966; Yamakado & Yohro, 1979). A minor group of labial vibrissa follicles develops later, near the margin of the upper lip. The vibrissa follicles of embryonic mice begin to appear on the snout at about 12 days of gestation (Grüneberg, 1943*b*), but the determinants of their precise location are unknown.

At the earliest stage of vibrissa follicle development which has been described (Stage 1; Davidson & Hardy, 1952), a follicle consists of a slight epidermal downgrowth into a mesenchymal condensation located directly beneath an epithelial

* Present address: Biology Department, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J1

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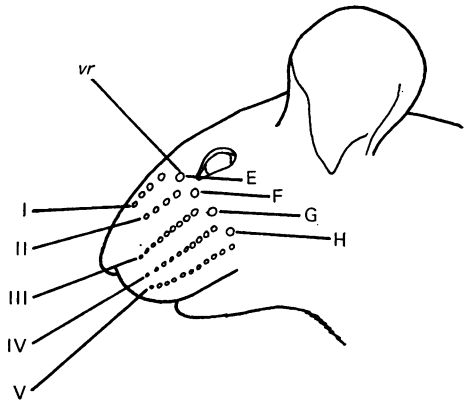



Fig. 1. Diagram of the head of an adult mouse showing the location of the mystacial vibrissae on the snout. Follicles E, F, G and H form the vertical row (*vr*). The five horizontal rows are designated by Roman numerals.

placode. Tello (1923) has demonstrated that a nerve plexus is located directly beneath the dermal condensation of each of these Stage 1 follicles in the 12 day mouse. He implied that these plexuses may be involved in determining the location of vibrissa follicle development. Kollar (1970) has demonstrated by tissue recombinations that there is a mesenchymal induction of the epithelium to initiate a follicle at some time prior to Stage 1 of follicle development; this interaction may also be involved in determining the location of vibrissa follicles.

However, little is known about the early morphogenetic events leading up to Stage 1. The purpose of this investigation was to study the development of follicles prior to Stage 1 and to determine the histological relationship between nerves, mesenchyme and epithelium during this period. Follicle development begins near the caudal margin of a 'whisker pad' and progresses towards the rostral border (Davidson & Hardy, 1952; Van Exan, 1976; Yamakado & Yohro, 1979). At 12 days gestation, only the most caudal of the mystacial vibrissae have developed to Stage 1 (Grüneberg, 1943*b*; Yamakado & Yohro, 1979). It was therefore possible to observe the sequence of morphological events from Stage 0 to Stage 1 by examination of serial sections cut through the snout of 12 day embryos from the rostral to the caudal end in planes perpendicular to the horizontal rows, and comparison of these with sections from older embryos.

## MATERIALS AND METHODS

Embryos of known ages (12, 13 and 14 days of gestation) were obtained from 8 hour matings of BALB/c mice. The females were inspected for vaginal plugs at the time of separation of the males, which was considered to be the beginning of day zero. The precise stage of development was determined by comparison of the external features of the embryos with those described by Grüneberg (1943*b*) and Theiler (1972).

The head of each embryo was removed and fixed in Smith's modification of Bouin's fluid (Guyer, 1953) for 24 hours. After routine dehydration and impreg-

nation, the heads of six embryos of each age were oriented in paraffin blocks and 7 $\mu$m serial sections were made through the entire snout perpendicular to the plane of the margin of the upper lip. The sets of sections from two embryos of each age were stained with haematoxylin, eosin and picric acid (HEP; Carter & Clarke, 1957). Sections from two more embryos of each age were stained with Mallory trichrome stain (Lillie, 1965) and sections of the remainder were stained with Ungewitter's urea silver nitrate stain (Thompson, 1966).

Serial reconstructions were made of the snout of six 12 day embryos by tracing the outline of each section onto a card with the aid of a Carl Zeiss drawing tube. The magnification of each tracing was 43 times the actual size of the section and the cards were approximately 43 times the thickness of the sections. Details of nerves, blood vessels and developing vibrissa follicles were marked on the tracings. After the traced outlines had been carefully cut with fine scissors, the cards were stacked in such a way as to reconstruct a model of the 12 day embryonic mouse snout. Comparison of the model with the snout of an intact litter mate permitted a reasonably accurate alignment of the cards. The histologically identified Stage 1 follicles were marked on the outside of the model and these were used, in combination with data on follicle location obtained from the older embryos and with Dun's (1958) description of follicle location in adult mice, to locate the areas of presumptive follicle development. These locations were also marked on the model before it was dismantled. The areas of presumptive follicle development were then examined in detail on the histological sections from which the model was constructed.

## OBSERVATIONS

The epidermis of the whisker pad in the 12 day embryo was somewhat thicker than that on the rest of the head and snout (Fig. 2*a*). The irregular layer of flattened cells forming the remainder of the snout epidermis (Fig. 2*b*) appeared less differentiated than the epidermis of the whisker pad (Fig. 2*c*), which was composed of a regularly arranged basal layer of columnar cells, and occasionally a second, incomplete layer of cuboidal cells. In both areas a flattened periderm layer covered the epidermis. At the edge of the whisker pad, between the two types of epidermis, was a narrow zone showing a gradual transition. This transitional zone was mainly composed of a single well organized layer of cuboidal cells beneath the periderm (Fig. 2*d*). The topographical distribution of these three types of ectoderm is shown in Figure 3*a*.

Unfixed embryos at this stage of development showed, under a stereoscopic microscope, four follicles in the vertical row and the first one or two follicles of the more ventral three horizontal rows of the mystacial group as small domes protruding from the whisker pad. One follicle of the vertical row (follicle H; Fig. 1) was in line with the fifth horizontal row (Fig. 3*b*).

The serial reconstructions from paraffin sections revealed five more or less parallel ridges which were evenly spaced across the whisker pad between its ventral and dorsal boundaries (Figs. 3*a*, 4), and which ran from its caudal end towards its rostral end, the two more dorsal ridges being much shorter than the others. The Stage 1 follicles of the horizontal rows were located at the caudal ends of these ridges. Three follicles of the vertical row (follicles E, F and G) were located between and just caudal to the ends of the four more dorsal ridges. Follicle H of the vertical row was located at the caudal end of the most ventral ridge yet remained in line with the other follicles of the vertical row (Fig. 3*b*). In the adult, this follicle was located

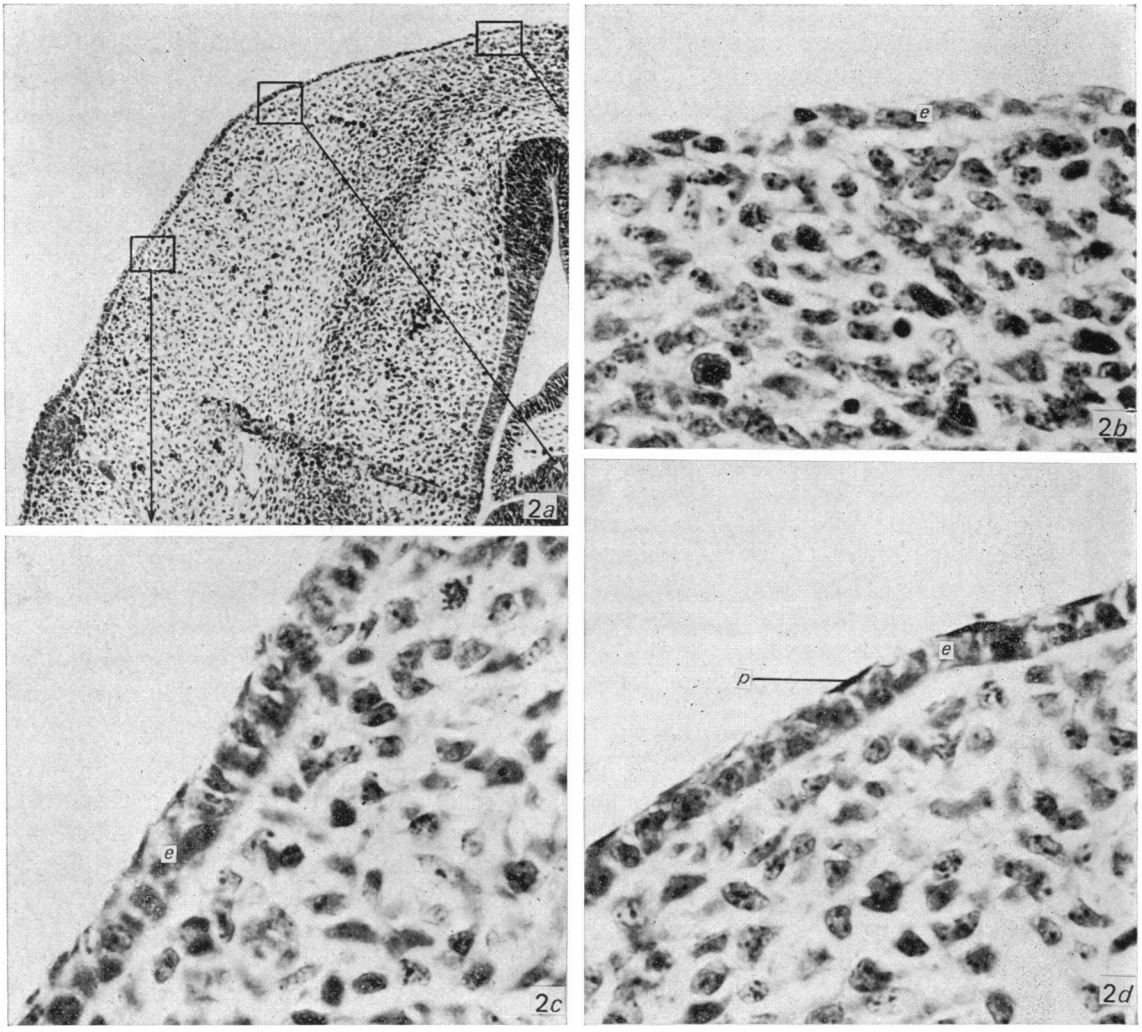



Fig. 2. Photomicrographs of a section through the snout of a 12 day mouse embryo in a plane perpendicular to the horizontal rows of vibrissa follicles. 7 $\mu$m. HEP. (*a*) Low power view of part of the left side of the snout. On the right side of the Figure are the nasal passages. The whisker pad occupies the more lateral two thirds of that part of the surface of the snout which is in the field of view. × 133. (The areas enclosed in boxes are seen at higher magnifications in (*b*), (*c*) and (*d*), as indicated by the arrows.) (*b*) Head epidermis (*e*),consisting of a loosely arranged single layer of slightly flattened epithelial cells, beneath a very flattened periderm. × 853. (*c*) Whisker pad epidermis (*e*), consisting of a well-organized single layer of columnar epithelial cells, beneath a flattened periderm. × 853. (*d*) Transitional epidermis (*e*), composed of cuboidal cells, beneath a flattened periderm (*p*). × 853.

between and just caudal to the fourth and fifth horizontal rows (Dun, 1958). Aside from this variation, the follicles and ridges corresponded in location to the rows of follicles found on the whisker pad of the adult mouse (compare Fig. 3*b* with Fig. 1).

The ventral border of the whisker pad was delineated by a shallow groove, parallel and just ventral to the fifth horizontal ridge (Fig. 4). It extended from near the ventral margin of the external naris to the vicinity of the third follicle from the caudal end

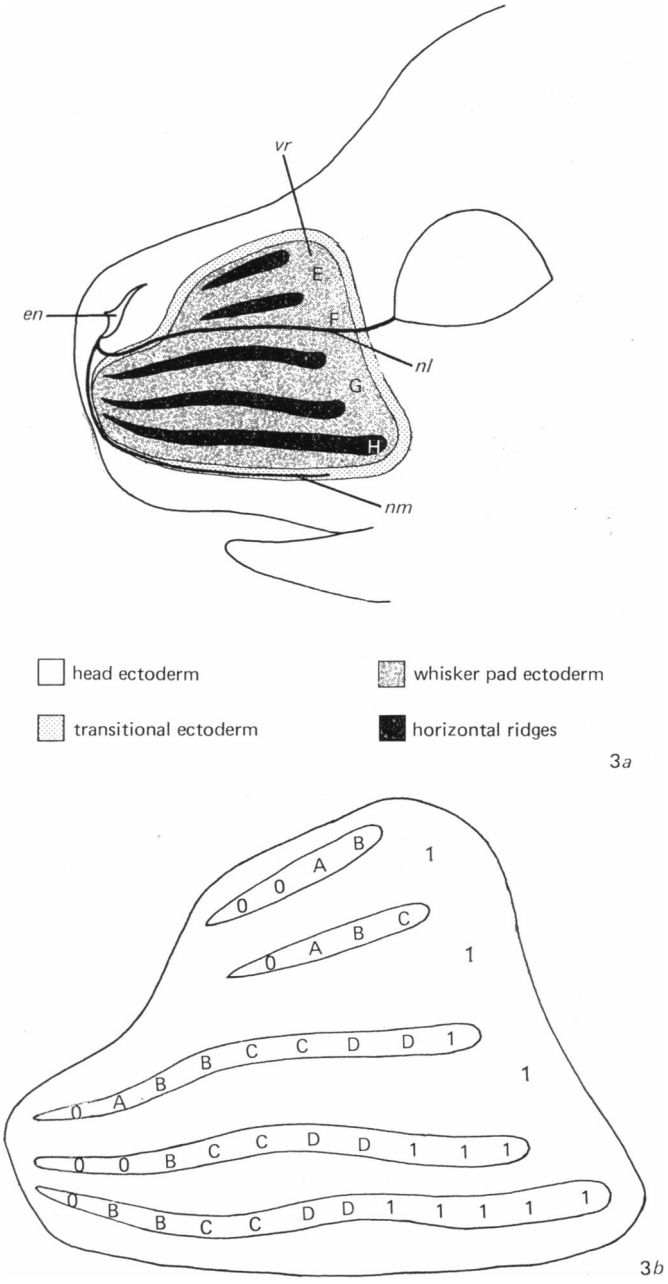
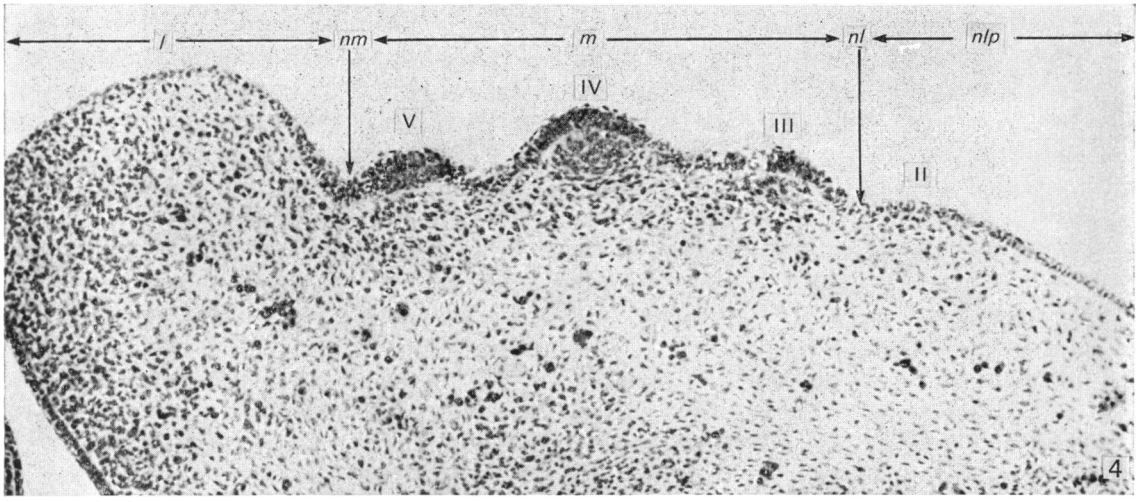



**Fig. 3(*a*). A diagram of the left lateral aspect of the head of a 12 day embryo prepared from observations made on several sets of serial sections and serial reconstructions. The different types of epithelium covering the snout (Fig. 2*b*, 2*c* and 2*d*) are indicated by the shading. The five horizontal skin ridges are shown in black. The nasolacrimal (*nl*) and masomaxillary (*nm*) grooves, shown as heavy lines, both originate from the lateral margin of the external naris (*en*), *vr*, vertical ridge. (*b*) An enlargement of the whisker pad shown in Fig. 3*a*. The stages of vibrissa follicle development (as summarized in Table 1) are indicated at each follicle locus. Note that follicle H of the vertical row is located at the end of the most ventral ridge. This location does not correspond with that observed in the adult (Fig. 1).**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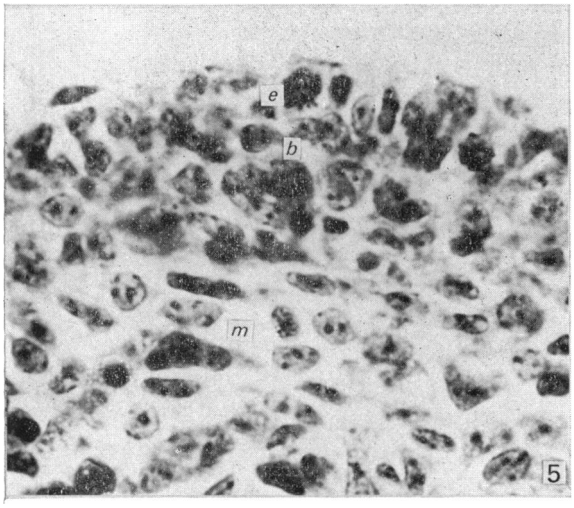
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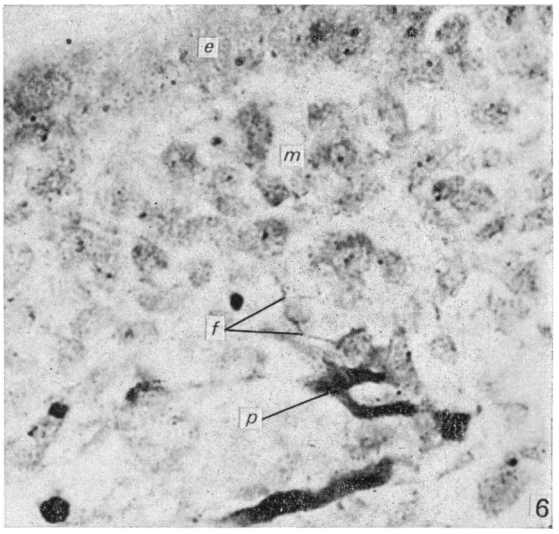
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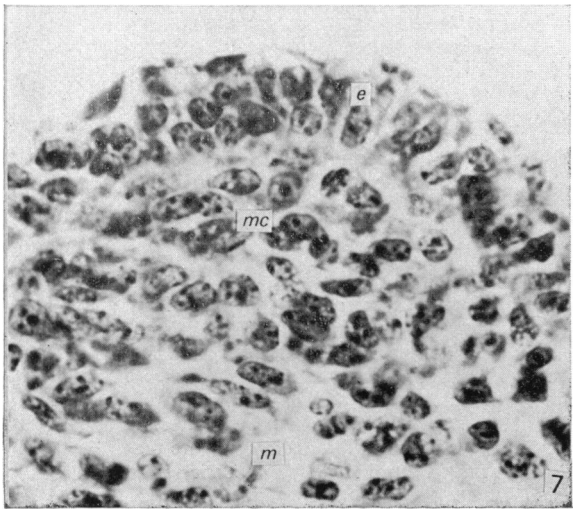
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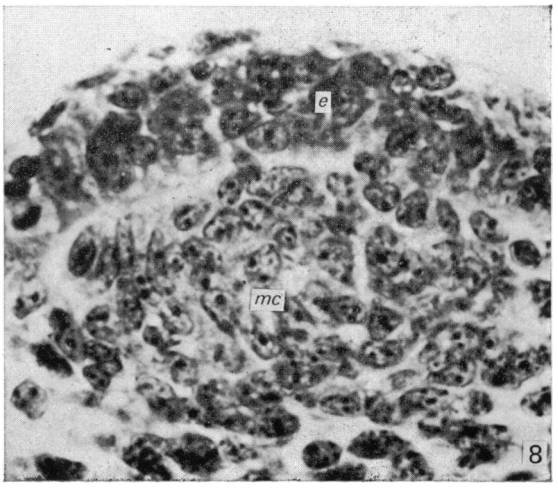
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of the fifth ridge (Fig. 3*a*). This 'nasomaxillary' groove divided the surface of the maxillary prominence into a major maxillary segment and a labial segment. The nasolacrimal groove lay between the second and third ridges just prior to 12 days of gestation (Figs. 3*a*, 4) and separated the major maxillary prominence from the nasolateral prominence.

By examining the models and the topographical distribution of developing follicles in older embryos and adult mice, it was possible to locate and mark on the model the locus of every future follicle. Once marked in this way, a model was used, in conjunction with the serial sections from which it was made, to identify all the structures which were at these loci.

Careful examination of the more rostral of the sections showed that the epidermis over each ridge was slightly thicker than the epidermis of the surrounding whisker pad, being two to three cells thick at the peak of the ridge (Fig. 5). Over the ridge the contour of the base of the epidermis was parallel to the contour of the outer surface of the epidermis, and the mesenchyme filling the inside of the ridge did not appear different from the mesenchyme underlying the rest of the whisker pad. This appearance was maintained in all the interfollicular regions along each ridge. The presumptive follicle loci at the rostral end of each ridge possessed the same structure. Since there was no morphological difference between these presumptive follicles and the interfollicular ridge at this time, the presumptive follicle loci were defined as *Stage 0* follicles.

As one moved caudad through the serial sections, the presumptive follicle loci began to exhibit a structure distinctly different from that of the interfollicular regions with respect to epidermal, mesenchymal and nervous elements. These morphological changes from the Stage 0 condition of follicle development will now be described in sequence (Table 1).

The first deviation from the Stage 0 structure in a presumptive follicle locus was observed in serial sections impregnated with silver. A very small nerve plexus derived from two small nerve trunks was observed under a presumptive follicle locus which otherwise possessed the same structure as a Stage 0 follicle. Even though there was

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Fig. 4. Photomicrograph of a section through the snout of a 12 day mouse embryo showing horizontal ridges II, III, IV and V in cross section. The left side of the snout is in the upper part of the photograph. Ridge V is located dorsal to the nasomaxillary groove (*nm*). This groove divides the maxillary prominence into its labial (*l*) and major maxillary (*m*) segments. The nasolacrimal groove (*nl*) is located between ridges II and III and separates the maxillary prominence from the nasolateral prominence (*nlp*). 7 $\mu$m. HEP. $\times$ 143.

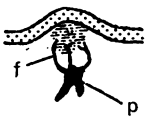
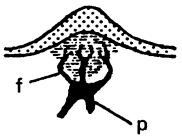
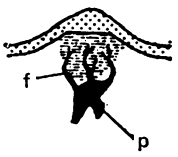
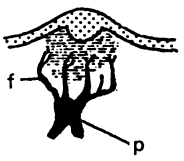
Fig. 5. Photomicrograph of a presumptive follicle locus (Stage 0) near the rostral end of the third ridge. The epithelium (*e*) is composed of two to three cell layers and is slightly thicker than that of the surrounding whisker pad (Fig. 2*c*). There is no more condensation of the mesenchyme (*m*) in this follicle locus than elsewhere in the ridge. *b*, basement membrane. 7 $\mu$m. HEP. $\times$ 853.

Fig. 6. The Stage A follicle in this photomicrograph differs from Stage 0 (Fig. 5) only in that it possesses a small nerve plexus (*p*). Fine nerve fibres (*f*) originating in the plexus penetrate the ridge mesenchyme (*m*) under the ridge epithelium (*e*). 7 $\mu$m. Ungewitter's urea silver nitrate. $\times$ 853.

Fig. 7. The epithelium (*e*) of this Stage B follicle is composed of two to three cell layers, as in earlier stages (Figs. 5, 6). However, a mesenchymal condensation (*mc*) has formed within the ridge, which has a higher cell density than interfollicular mesenchyme or underlying mesenchyme (*m*). 7 $\mu$m. HEP. $\times$ 853.

Fig. 8. The epithelium (*e*) of this Stage C follicle is thicker than at previous stages of development (Figs. 5, 7). The mesenchymal condensation (*mc*) has increased in cell density. 7 $\mu$m. HEP. $\times$ 853.

Table 1. *A summary of the early stages of vibrissa follicle development in the mouse*

| Stage | Characteristics | Structure |
|---|---|---|
| Stage 0 | No difference between follicular and interfollicular regions of the skin ridge |  |
| Stage A | Nerve plexus forms under ridge, fine fibres penetrate ridge mesenchyme |  |
| Stage B | Nerve plexus larger, nerve fibres more extensive, mesenchymal condensation forms over plexus |  |
| Stage C | Nerve plexus larger, nerve fibres thicker, mesenchymal condensation denser, thickening of epithelium over dermal condensation |  |
| Stage D | Nerve fibres from plexus are thicker, mesenchymal condensation larger, basal layer of epithelium becomes flat across the ridge. |  |
| Stage 1 | Nerve fibres from plexus are longer, epithelium grows down into mesenchymal condensation |  |

▤, epithelium. ▤, mesenchymal condensation. p, nerve plexus. f, nerve fibre.

no mesenchymal condensation, a few fine fibres were observed extending from the nerve plexus into the mesenchyme of the ridge (Fig. 6). This presumptive follicle was termed a *Stage A* follicle. Adjacent interfollicular regions of the ridge never contained nerve fibres or plexuses.

As ridges were traced caudad, no changes were observed in the epidermis, but within the regions of presumptive follicle development the mesenchyme had a slightly greater cellular density than the surrounding mesenchyme. These regions were defined as *Stage B* follicles (Fig. 7) and they were clearly separated from each other by interfollicular regions of the ridge.

Further caudad the epidermis was observed to be slightly thicker (two to four cells) in the presumptive follicle loci, which were now termed *Stage C* follicles (Fig. 8). Directly under these epidermal thickenings, the mesenchyme was observed to be distinctly more dense than the surrounding mesenchyme. The mesenchymal condensations filled the ridge and extended below it as a cone of densely packed cells terminating just above the nerve plexus. The epidermis of these Stage C follicles did not extend down into the mesenchymal condensation. The Stage C follicles were

fairly well demarcated, being separated from each other along the ridge by regions of unmodified interfollicular ridge.

Each Stage B and Stage C follicle also possessed a nerve plexus formed from the union of at least two nerve trunks directly under the dermal condensation, which was surrounded and penetrated by fine nerve fibres (Fig. 9).

Still further caudad, presumptive follicles defined as *Stage D* were observed on ridges III, IV and V. They were identified by a thickening of the epidermis of the ridge, the basal layer of which no longer followed the contour of the outer layer, but rather was flattened, cutting across the top of the ridge (Fig. 10). There was a mesenchymal condensation directly under each epidermal thickening which was of the same shape as those of the Stage C follicles.

Typical *Stage 1* follicles were located at the caudal end of ridges III, IV and V. These follicles exhibited an actual downgrowth of the epithelium of the ridge into the mesenchymal condensation, which was very conspicuous at this stage (Fig. 11).

The nerve plexuses of the Stage D and Stage 1 follicles were larger and more complex than those observed at the earlier stages of development (Fig. 12). Although nerve fibres were observed extending from the plexus into the mesenchymal condensation at each stage of follicle development, they were never observed in direct contact with the epithelium.

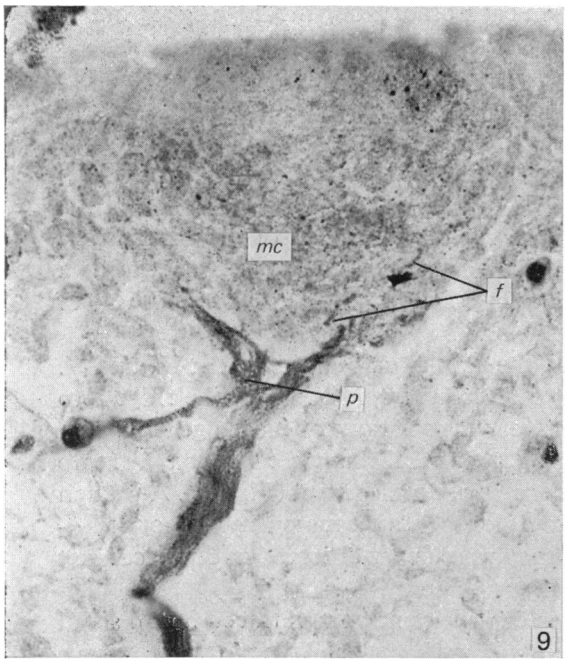
The nerve supply of follicles at all stages of development was traced in the serial sections. The five major branches of the maxillary branch of the trigeminal nerve lay deep in the mesenchyme beneath the five ridges, as shown by Tello (1923). Each plexus appeared to be derived from two or more nerve trunks originating from these branches.

From the above observations a map of the snout of the 12 day embryo was constructed showing the differentiation of the epidermis (Fig. 3*a*) and the stage of each follicle at this age (Fig. 3*b*).

## DISCUSSION

Since the above observations were completed, the tactile hairs located on the snout of the mouse have been divided into three major groups on the basis of embryological origin (Yamakado & Yohro, 1979). The nasolateral group (horizontal rows 1 and 2) develop from a growth centre on the nasolateral prominence. The maxillary group (horizontal rows 3, 4 and 5) and the labial group develop from two different growth centres on the maxillary prominence (Streeter, 1948). It has recently been shown by scanning electron microscopy that the nasolateral and the maxillary groups are separated at about 12 days by the nasolacrimal groove (Yamakado & Yohro, 1979). The present study has shown that the labial group is also separated by a groove (nasomaxillary) from the maxillary group at about 12 days of gestation. Thus the three growth centres for tactile hairs appear to be morphologically separated by two shallow grooves at the time when the follicles are just beginning to develop. It appears that the cortical barrels of the somatosensory cortex are also divided into three groups, each making connections with one of the three groups of follicles (Yamakado & Yohro, 1979).

The present study has demonstrated that the mystacial vibrissae of the mouse develop in the first instance from ridges of skin rather than from individual placodes as do the pelage follicles (Montagna & Ellis, 1958). Our observations indicate that the more rostral parts of the ridges form prior to Stage A of follicle development in that region (i.e. prior to plexus formation). It seems likely, from the observations of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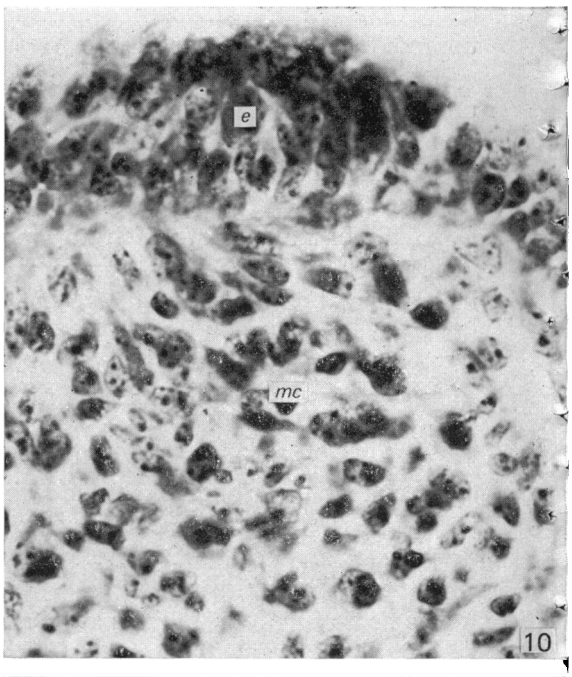
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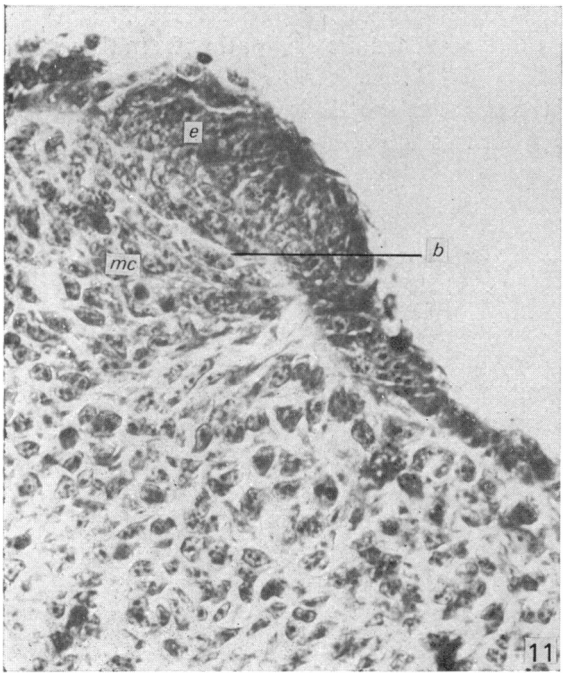
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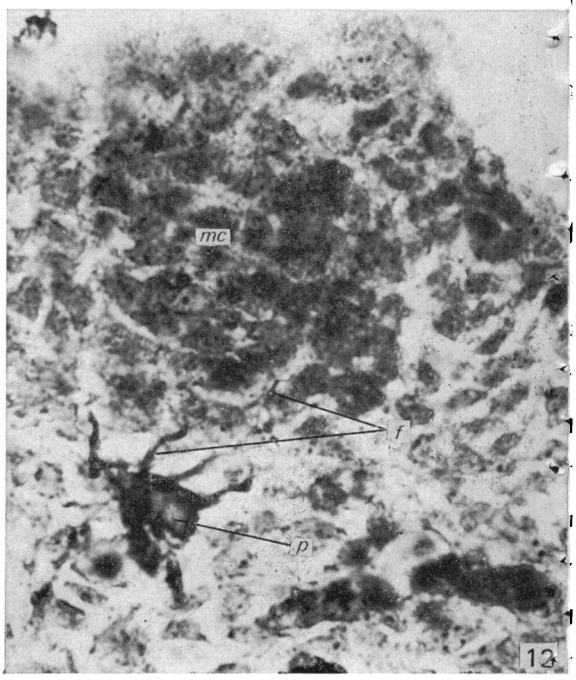
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Tello (1923) and Yamakado & Yohro (1979) on younger embryos, that ridge formation precedes Stage A of follicle development on all parts of the whisker pad.

The development of the five horizontal rows of mystacial vibrissae from the five horizontal ridges suggests that the ridges may play a role in establishing the linear array of the follicles on the snout. Other ectodermally derived organs which have a linear arrangement, such as teeth and mammary glands, also develop from ridges. The teeth develop from the dental laminae, epithelial ridges in the regions of the upper and lower jaws (Hamilton & Mossmann, 1972), and mammary glands develop from the skin along the mammary lines (Graumann, 1950). It would appear, therefore, that the formation of the ridges is a rather common developmental mechanism for aligning epithelially derived organs in specific patterns. In each instance, the organs (vibrissae, teeth, mammary glands) develop at more or less regular intervals along the ridge.

On the snout the horizontal ridges were formed by folding of a plate of ectoderm (the whisker pad) which was slightly thicker and better differentiated than the surrounding ectoderm. Similarly, the mammary lines lay on wider strips of thickened ectoderm called the mammary bands (Schmidt, 1898). The significance of the ectodermal thickening of whisker pads and mammary bands is unknown. It may perhaps indicate a morphogenetic event important to the formation of the ridges. Ectodermal competence to produce vibrissa follicles is not restricted to the thickened epithelium of the whisker pad, since even dorsal trunk epidermis has the potential to develop vibrissa follicles when recombined with 12·5 day whisker pad mesenchyme (Dhouailly, 1977). Dhouailly's observations suggest that the ridge epithelium is not the sole determinant of the location of follicle development. Some other factor must determine the precise location of the follicles along the ridge.

After the formation of the ridges, the first event observed in follicle development was the formation of a nerve plexus directly beneath each presumptive follicle locus (Stage A). This occurred before any morphological changes were observed in the epithelium or mesenchyme of the ridge. It is therefore tempting to speculate with Tello (1923) that the nerve endings determine the location of vibrissa follicle formation.

It has been shown that nervous tissue can stimulate the development of feather follicle primordia in the chick. Skin explanted from chick embryos younger than 6 days of gestation does not form feather follicles in standard culture medium (Sengel, 1958). However, the feather primordia develop when skin is cultured in association with a piece of brain or spinal cord (Sengel, 1958) or their extracts (Sengel, 1961; Sengel & Feigelson, 1963). Sengel (1975) suggested that brain extract acted to

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Fig. 9. The nerve plexus (*p*) of this Stage C follicle is considerably larger than the Stage A nerve plexus (Fig. 6). Fine nerve fibres (*f*) surround and penetrate the mesenchymal condensation (*mc*), 7 $\mu$m. Ungewitter's urea silver nitrate. × 682.

Fig. 10. The Stage D follicle shown in this photomicrograph has a thickened epithelial cap (*e*) over the mesenchymal condensation (*mc*). Note that the basal layer of the epithelium no longer follows the contour of the outer epithelial surface, but rather is flattened, cutting across the top of the ridge. 7 $\mu$m. HEP. × 853.

Fig. 11. The epithelium (*e*) of the Stage 1 follicle has begun to grow down into the mesenchymal condensation (*mc*). *b*, basement membrane. 7 $\mu$m. Mallory trichrome. × 682.

Fig. 12. The nerve plexus (*p*) of this Stage D follicle is well developed, with thick nerve fibres (*f*) forming a network around and smaller fibres penetrating the mesenchymal condensation (*mc*). 7 $\mu$m. Ungewitter's urea silver nitrate. × 853.

maintain the organic integrity of the skin in culture, triggered off the differentiation of the feather rudiments, and stimulated growth, resulting in the formation of typical feather filaments. It appears that the effect of the nervous tissue in feather formation is somewhat similar to an inductive one, since the extract is not required after the primordia have begun to develop (Sengel, 1964, 1975). Although extracts of other organs were also found to stimulate the development of feather primordia in chick skin (Sengel, 1975), they were less effective. They may have contained smaller amounts of some chemical substance produced by the nervous tissue.

The incidence of tooth germ development in cultures of mandibular tissue was increased if the trigeminal ganglion was included in the explants (Kollar, 1976). Kollar & Lumsden (1979) were also able to demonstrate nerve endings in the regions of presumptive tooth development prior to the formation of the tooth primordia. They suggested that the spatial pattern of tooth development may be determined by the innervation of sites along the dental laminae during an initiation phase prior to morphogenesis. It has also been established that nerves play an important role in the development and regeneration of taste buds (Farbman, 1972; Zalewski, 1974). There is therefore some circumstantial evidence supporting the hypothesis that nerves normally play a role in initiating the formation of the mesenchymal and/or epithelial primordia of some epithelially derived organs.

In vibrissa follicle development, the formation of a mesenchymal cell condensation (Stage B) follows plexus formation. Proof that these two events are causally related is lacking, but it is conceivable, for example, that a substance secreted by the nerve endings is responsible for the aggregation of the mesenchyme cells.

The next step, epidermal thickening above the mesenchymal condensation (Stage C), was probably the result of the mesenchymal induction demonstrated by Kollar (1970). The timing of this event is thus now more precisely defined. It is possible that the nervous elements may play a part in this interaction also.

The epidermis responded during Stage D, Stage 1 and later stages by forming the type of follicle (i.e. vibrissa) which had been earlier determined by its own regional origin (Kollar, 1970; Dhouailly, 1977). It is less likely that nervous tissue played an instructive role in these stages, since these changes could take place normally *in vitro* when nerve endings were absent or degenerating (Davidson & Hardy, 1952; Van Exan, 1979).

## SUMMARY

The present study has demonstrated that the mystacial vibrissae of the mouse began to develop at about 12 days of gestation on two plates of thickened ectoderm called the 'whisker pads' which were located on either side of the snout above the margin of the upper lip. Each whisker pad was traversed by five rostrocaudal skin ridges. The individual vibrissae developed along the ridges in a caudorostral sequence.

Four new sub-stages of vibrissa follicle development which occurred prior to Stage 1 of Davidson & Hardy (1952) were described. The first of these, Stage A, was the formation of a small nerve plexus under the skin ridge. Stage B was then characterized by the formation of a dermal condensation above the nerve plexus. The epithelium over the dermal condensation began to thicken at Stage C and grow down into the dermal condensation at Stage D.

The early morphogenesis of the mystacial vibrissa follicles of the mouse was compared to that of teeth and mammary glands. The possibility of nerve involvement in determining the pattern of follicle array on the snout was discussed. The sequence

of the morphological changes in the dermal and epidermal components of the early follicles was related to the present knowledge of epithelial–mesenchymal interactions which occur during this phase of follicle development.

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