STUDIES ON THE FOLLICLE BULB OF FIBRES

I. MITOTIC AND CELLULAR SEGMENTATION IN THE WOOL FOLLICLE WITH REFERENCE TO ORTHO- AND PARASEGMENTATION

By I. E. B. FRASER*

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Summary

There is a gradient in the density of cells in mitosis which decreases in a proximodistal direction. Mitotic activity ends at a height one cell layer above the apex of the papilla. The decreasing mitotic density gradient commences at a level, in all bulbs, coincident with the proximal limit of differentiation of Henle's layer of the inner root sheath.

In follicles which tend to be straight, and in which Henle's layer keratinizes evenly around the equator of the bulb, mitotic "activity" tends to be localized around the papilla apex in the distal half of the germinative region. The position of the ortho- and paracortex in fibres from such follicles is very irregular, ranging from scattered clumps of paracortex to peripherally and axially situated paracortex.

In deflected bulbs, in which Henle's layer keratinizes more proximally on the ental side than on the ectal side of the bulb deflection, a bilateral mitotic and cellular segmentation occurs within the germinative region. The ortho- and paracortex in fibres from such follicles are always bilaterally arranged.

I. INTRODUCTION

Since Horio and Kondo's (1953) demonstration of the bilateral structure of the cortex of wool fibres, much has been published on the differential response of the ortho- and paracortical segments (R. D. B. Fraser and Rogers 1953, 1954, 1955, 1956*a*; R. D. B. Fraser, Lindley, and Rogers 1954; R. D. B. Fraser and Macrae 1956; Gillespie and Lennox 1953; Mercer 1953; Dusenbury and Coe 1955; Golden, Whitwell, and Mercer 1955; Simmonds 1955; Dusenbury and Menkart 1956; Ahmad and Lang 1957; Menkart and Coe 1958). The combined work of these authors indicates that the differing reactivity of segments of the fibre cortex is manifested in its effect on dye uptake, enzymic hydrolysis, and chemical composition, particularly cystine.

On the basis of the differential in cystine content of the two segments, Mercer (1954) suggested that bilateral structure was the result of uneven keratinization in the follicle. But R. D. B. Fraser and Rogers (1956*a*) disproved this by showing that bilateral structure of the fibre is observable in the follicle well below the level of fibre keratinization, and went so far as to suggest that the predetermination of ortho- and paracortical cells (S and H segments respectively) was likely to occur below that level in the follicle at which they could demonstrate segmental cortical structure. They proposed that bilateral segmentation of the fibre cortex originated at the germinal level within the bulb matrix, though they could not substantiate this.

* Lincoln College, University of Canterbury, N.Z.; present address: Wool Research Organization of New Zealand (Inc.), Christchurch, N.Z.

Before any published report of ortho- and paracortical cell segmentation appeared, Auber (1951) in his description of the anatomy of the wool follicle reported on certain cellular details of the follicle bulb. He showed that two cell types could be distinguished within follicle bulb tissue:

(1) Cells in the proximal bulb region which were capable of mitosis and which were non-differentiating; and

(2) Cells in the distal bulb region, up to the papilla apex, which were differentiating cells and not exhibiting mitotic activity.

Further, Auber observed that in deflected bulbs the undifferentiated cells extended further distally on the ectal side of the bulb deflection than on the ental side (Auber 1951, Plate II,*d*).

In the light of the suggestions put forward by R. D. B. Fraser and Rogers (1956*a*) the observations made by Auber (loc. cit.) warranted further and more extensive investigation. In order to achieve this a large number of wool follicles from Romney sheep were investigated histologically. The pattern of mitotic activity and cellular differentiation within different wool follicle bulbs has been observed and such patterns have been considered in relation to the position of the ortho- and paracortical cells of the fibre cortex.

II. Terminology

The term *matrix tissue* has been used in the past to define two different components of a hair or wool follicle. Firstly, the term refers to that part of the follicle bulb that is the germination centre of the follicle where every cell is mitotically active (Bullough and Lawrence 1958; Montagna and Van Scott 1958), and secondly, the term refers to the amorphous "cementing" material within the fibre in which the cortical cells are embedded (Astbury and Dickinson 1940; Alexander and Hudson 1954; Rogers 1959). Though the definition of *matrix* is given in the Oxford English Dictionary as (*a*) a place or point of origin or growth, or (*b*) an embedding or enclosing mass, the use of the same term for totally different structures in hair and wool follicles is confusing. For this reason alone it is considered that a change in the terminology would be to advantage. As its use in defining a packing material or enclosing mass is most widely used it is preferable to use an alternative term for defining the matrix of the follicle bulb.

The use of the term matrix in defining the limits of the matrix tissue in the follicle bulb has in itself lead to confusion. Some workers investigating the bulb tissue of follicles producing medullated fibres (e.g. rat, mouse, and human skin follicles) use the term matrix to define all of the bulb tissue between the proximal and distal papilla levels, excluding the papilla tissue (Bullough and Lawrence 1958). Other workers define the limits of the matrix tissue of such follicles more critically (Montagna and Van Scott 1958) as being the bulb tissue below the *critical level* (Auber 1951) of the papilla. None of the above workers, however, has shown irrefutably that all cells within the respective matrices are capable of mitosis, as the accepted use of the term matrix requires. However, Bullough and Lawrence (1958) assume that all cells within the follicle bulbs in the skin of mice between the proximal and distal limits of the papilla are capable of mitosis.

As a result of the investigations described below, the bulb tissue of wool follicles between the proximal and distal limits of the papilla, excluding the papilla tissue, is described as the *germinative region* in preference to the term matrix. This region contains *mitotic cells* and *differentiating cells*. In non-medullated follicles the differentiating cells will be root sheath cells and cortical cells, whilst in medullated follicles medullary cells will be a further type of differentiated cell. There is no definite evidence that medullary cells are mitotically active.

III. Experimental

The location of sites of mitotic activity within the germinative region are successfully obtained by the stasis of mitosis using either colchicine or colcemid. As colcemid has many advantages over colchicine when used for injection into sheep, and achieves the same degree of mitotic stasis in the dividing cells of wool follicle bulbs (I. E. B. Fraser 1963), it has been used during this work.

After induction of mitotic stasis over a period of 6 hr, a measure of mitotic activity is generally obtained by computing the mitotic index. The mitotic index is the ratio of the number of cells in mitosis to the total number of cells in the population. In view of the difficulty of measuring the total number of cells in the germinative region of wool follicle bulbs, the mitotic density* has been determined to give a measure of mitotic activity. The mitotic density is the number of cells in mitosis per unit volume of the germinative region and is expressed as the number of mitotic cells in 10^4 cubic microns.

IV. Material and Methods

A dose of 0·35 mg/kg body weight of colcemid in 10 ml sterile water was injected into the jugular vein of Romney wethers and a Merino ewe. After 6 hr skin samples were excised from mid-side body positions and fixed (I. E. B. Fraser 1963). Longitudinal tissue sections were cut along the axis of the follicle, and transverse sections in serial sequence were cut at 6 μ at right angles to the long axis of the papilla throughout the thickness of the skin up to sebaceous gland level. In order to achieve the latter, reducing the possibility of oblique sectioning to a minimum, the tissue blocks were carefully positioned and repositioned on the microtome. The follicle bulbs used in this work had the following specifications:

(1) They were circular or only slightly elliptical in cross-section;

(2) They showed papilla tissue within the formation of the bulb in either of the first two 6 μ sections at the proximal bulb end;

(3) They did not show signs of oblique cutting, as discerned from cell detail across the diameter of the bulb.

Tissue sections were oxidized in formic acid (9 : 1 v/v of 20% formic acid and 30% hydrogen peroxide respectively) for 30 min at room temperature. The sections were then stained for mitoses using Weigert's haematoxylin (2–5 min). After bringing down to water, all sections were stained with a 1% solution of methylene blue

* This term is used in preference to "mitotic ratio" as used earlier (I.E.B. Fraser 1963).

(Polychrome) in acetate buffer (pH 2·64) for 2–5 min at room temperature, to distinguish ortho- and paracortex. After differentiation in 1% HCl in 70% ethanol the sections were counterstained in 0·5% ethanolic eosin.

In transverse sections, deflected and straight follicle bulbs were identified according to Auber (1951) by the position of the initial differentiation of the inner root sheath. In medial longitudinal sections the presence or absence of deflection is clearly observable.

The number of mitoses were counted in each serial section of individual follicle bulbs to obtain the total number of mitoses in the germinative region of each follicle bulb. The number of nuclei as well as the number of mitoses were counted in some bulbs so as to compute the mitotic index. In the follicles used for the examination of ortho- and paracortex, serial sections were followed from the bulb up to a level in the follicle where the ortho- and paracortex of the fibre were differentiated.

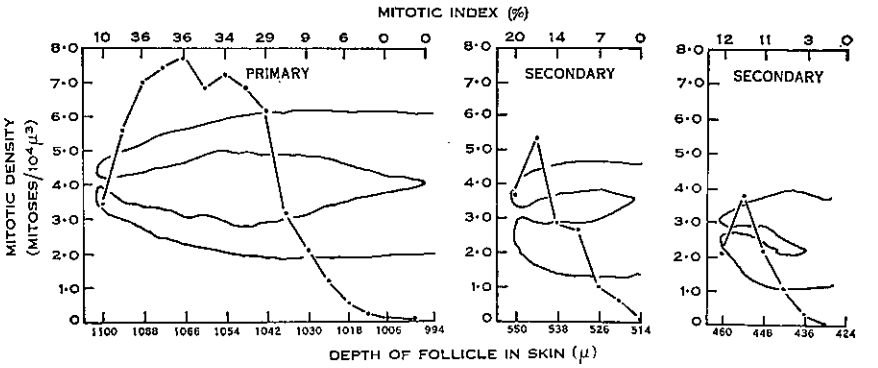

Fig. 1.—Mitotic density and mitotic index values at different bulb levels in different Romney sheep. Each follicle is located at a different skin depth. The mitotic index is the number of mitotic cells expressed as a percentage of total cells.

Bulb tissue area measurements on sections in serial progression, proximodistally, were obtained by planimeter measurement of tracings from projected (×260) slides. From such area measurements and known section thickness, the volume of the germinative region of follicles was calculated (I. E. B. Fraser 1963).

V. Results

(*a*) *Mitotic Activity Gradient*

Investigation of over 1000 follicles from three different Romney sheep shows that mitotic activity decreases proximodistally in all bulbs.

The primary and two secondary follicles of differing bulb volumes which have been drawn in section in Figure 1 were taken from three different sheep at different skin levels. The proximodistal gradients in mitotic density and mitotic index (at 6- and 12-μ intervals, respectively, within the germinative region) are characteristic to a greater or lesser degree of all follicles studied. From mitotic

density and mitotic index values (see Fig. 1) it seems that mitotic density is high in the proximal half of the bulb and is reduced in the distal half, falling to zero in the vicinity of the papilla apex.

The difference in mitotic density shown in Figure 1 is due to the difference between sheep and is not a consequence of follicle size within one sheep (Fraser, unpublished data).

The different mitotic indices of primary and secondary follicles clearly show that the cells of the germinative region are not mitotically equipotent. When the mitotic activities of the proximal half of the follicle bulb regions of primary and secondary follicles (i.e. the sites of maximal mitotic activity) are compared (Fig. 1) it can be seen that the mean number of cells arrested at metaphase (6 hr) in primary follicles is 30% compared with 16·8% in the same period in secondary follicles. Assuming that colcemid does not affect the number of cells entering division, this means that of the cells in the proximal half of the germinative region of primary follicles approximately 5% undergo division per hour, and approximately 2·8% divide per hour in secondary follicles. On this basis it can be estimated that at the time of year when these skin samples were taken (March) each primary follicle cell was undergoing division once in 24 hr, and each secondary follicle cell once in 36 hr. These values of 5·0% and 2·8% may be too low as the work of Hell and Cox (1963) casts doubt on the validity of the assumption that colcemid does not affect the number of cells entering division.

In accord with results of other observations on the wool follicle (Auber 1951) and other mammalian hair-bearing follicles (Chase 1954), cell division is not restricted to the basal cells of the matrix.

(*b*) *Localization of Mitoses within the Follicle Germinative Region*

The variation of mitotic density proximodistally within the germinative region depicted graphically in Figure 1 is exemplified by the tissue sections in Plates 1–3, though the decrease follows a different pattern in different follicles. These follicles are typical of those found in Romney sheep, that in Plate 1, Figure 1, of a deflected bulb and that in Plate 1, Figure 2, of a bulb tending to be straight.

In the deflected bulb (Plate 1, Fig. 1), reduction in the number of mitoses occurs as a consequence of the progressive localization, proximodistally, of the dividing cells on the ectal side of the bulb deflection. This phenomenon is again clearly shown in serial sections of the germinative region (Plate 2, Figs. 1–9) cut as near to right angles to the long axis of the papilla as the abovementioned technique (see Section IV) allowed.

In the follicles which tend to be straight (Plate 1, Fig. 2), the obvious bilateral segmental localization of dividing cells within the germinative region does not occur. The reduction in the number of dividing cells falls off on each side of the papilla (Plate 1, Fig. 2; Plate 3, Figs. 1–9).

In observations of over 1000 follicles from Romney sheep, the localization of cell division on each side of the papillae was consistently associated with the level of the commencement of keratinization and differentiation of the inner root sheath.

The deflected bulbs, in which the inner root sheath becomes picrophilous entally at a more proximal position than ectally (Plate 1, Fig. 1), cease cell division on the ental side as the picrophilous reaction moves around and up the follicle bulb. In such follicles, mitotic "activity" is retained on the ectal side (Plate 2, Figs. 1–9), where keratinization has not commenced. All mitotic "activity" ceases near the apex of the papilla, generally one cell layer above the papilla apex (Plate 2, Fig. 9). As a result of the segmental cessation of cell division on the ental side of the bulb, cells on this side of the follicle begin to grow and differentiate, cell walls becoming obvious (Plate 1, Fig. 1; Plate 2, Figs. 1–9). As a consequence of this, mitotic and cellular bilateral segmentation is observed within the bulb tissue.

In follicles tending to be straight, the picrophilous reaction of the inner root sheath occurs at approximately the same level of the bulb on both sides (Plate 1, Fig. 2) at a level approximately half-way up the papilla, as Auber (1951) has already shown. Distal to this level, cell division becomes localized axially within the follicle (Plate 3, Figs. 1–9).

(*c*) *Mitotic and Cellular Segmentation of the Germinative Region in Relation to Segmentation of the Fibre Cortex*

Segmentation of the fibre cortex in Romney sheep is very varied ranging from bilateral deposition of ortho- and paracortical segments to very irregular deposition of both (Plate 4, Fig. 1). Bilateral segmentation of the fibre cortex occurs in all follicles from Romney sheep exhibiting bilateral mitotic and cellular segmentation (cf. Figures 3 and 4 of Plate 4, which show sections from the same follicle which have been cut at right angles to the follicle axis). The section in Plate 4, Figure 3, is from the level where mitotic and cellular segmentation is evident, and the section in Plate 4, Figure 4, is from that level in the follicle at which ortho- and paracortical bilateral segmentation has occurred in the fibre cortex. This pair of sections demonstrates that the bulb segment retaining mitotic "activity" is on the same side of deflected follicles as the paracortex of the fibre. This is further verified in the medial longitudinal follicle section in Plate 4, Figure 2. The same phenomenon has also been observed in Merino follicles.

In all follicles which tend to be straight the pattern of cell division and cellular differentiation has not the same definite relation to the position of the ortho- and paracortex as in follicles with deflected bulbs.

In Plate 5, are shown two sections from each of two follicles (Figs. 1 and 2, and Figs. 3 and 4, respectively); one section from each follicle is from the distal level of the germinative region (Plate 5, Figs. 1 and 3) and one section from each follicle is from the level where fibre ortho- and paracortex can be demonstrated (Plate 5, Figs. 2 and 4). Both follicles at bulb level show a wide dispersal of mitotic cells with a tendency for an axial arrangement about the papilla apex. In the fibres within the same follicles, ortho- and paracortical differentiation is very irregular. Each fibre has a different type of para- and orthocortical pattern, but neither of them show bilateral segmentation. Such irregularity and lack of bilateral segmentation was observed in all follicles which tended to be straight.

VI. Discussion

The results fully substantiate observations that cell division within the wool follicle is not restricted to the basal cells surrounding the papilla (Auber 1951; Schinckel 1961).

The results presented also show that though it has been assumed that the follicle matrix of mice is equipotent throughout its volume (Bullough and Lawrence 1958), this is not the case in wool follicles.

The consistent association of mitotic and cellular bilateral segmentation of the germinative region of the bulb with bilateral segmentation of the ortho- and paracortex of the fibre strongly suggests that the initial site of the ortho- and paracortical cell differentiation of the fibre in deflected follicles has been positively located. It was shown (R. D. B. Fraser and Rogers 1956*a*) that cortical cell types resulting in H (hard) and S (soft) (para- and orthocortex respectively) bilateral fibre segmentation were differentiated below the zone of keratinization. Such results disproved the view held by Mercer (1954) that uneven keratinization in the follicle resulted in bilateral structure. On the basis of their observations, R. D. B. Fraser and Rogers (loc. cit.) suggested that predetermination of cells forming the para- and orthocortical segments was likely to occur at the germinal level in the follicle bulb, though they could not positively demonstrate this.

The results presented indicate that, in the case of the deflected bulbs, the cells on the ectal side of the germinative region (i.e. those maintaining mitotic "activity") correspond in follicular position to the paracortex of the fibre on the thin side of the follicle, whilst those on the ental side (i.e. differentiating cells) correspond in follicular position to orthocortical cells. The only alternative to this situation is if both cellular segments twist through 180° between the apex of the papilla and the level within the follicle at which the first signs of segmentation of the ortho- and paracortex are detected by the use of methylene blue. However, R. D. B. Fraser and Rogers (1956*a*) have demonstrated, by use of a birefringence technique, that the paracortex remains on the thin-walled side of the follicle, at a level close to the apex of the papilla, and well below that at which the methylene blue reaction first occurs. Thus, if a twist through 180° does occur it will be restricted to a position immediately above the papilla apex. As continuous bilateral cellular segmentation is not observable above the papilla apex (Plate 6, Fig. 1) it is not possible to show with certainty that the cells twist through 180° as they move proximally above the papilla apex, though this impression is gained (Plate 6, Fig. 1).

Despite the lack of definite evidence in favour of a twisting of cellular segments, it is tempting to postulate such a movement in view of the likely differential in cell growth rate between the two cellular segments.

In a recent attempt to explain crimp formation, Mercer (1961, pp. 157–8) assumes that the segmentation of the germinative region reported here does occur. On the assumption of a differential in cell growth rate between the presumptive ortho- and paracortex cells, he proposes that a 180° twist of each segment does occur above the papilla apex. Further, his theory requires that crimped, bilaterally

segmented fibres are grown within very idealized S-shaped follicles. During this investigation of many hundreds of follicles, and in other follicle investigations (Henderson, unpublished data) such a follicle form has never been observed. Even if Mercer's proposed follicle shape is found it is unlikely to bear any relationship to normal as such a follicle form presupposes a gross number of crimps per inch. In such sheep as the Romney and the Merino investigated during this work, with follicle lengths ranging from 700 to 1500 μ and from 500 to 800 μ respectively, and with fibre keratinization occurring at least one-third the way up the follicle (Burns and Clarkson 1949; Auber 1951), the number of crimps per inch would range between 40 and 90 for Romney, and 70 and 127 for Merino fibres. Such values are far in excess of normal values (Lang 1947).

In the case of straight follicles, the cells of the germinative region retaining mitotic activity at distal papilla level tend to be randomly dispersed, or more axially localized. The ortho- and paracortical cells of the fibres from such follicles do not occur in positions as clearly associated with the pattern of mitotic activity as in the deflected bulbs. Follicle bulbs with mitotic cells localized axially, and cell growth and differentiation occurring peripherally in the distal zone of the germinative region, do not necessarily produce fibres with an axial para- or orthocortex. In Plate 5, Figures 1 and 2, such a bulb is shown to produce a fibre with paracortex on two sides, neither of which is adjacent to the thin wall of the follicle. In Plate 5, Figures 3 and 4, the follicle bulb is associated with a fibre showing an axial localization of paracortex. The occurrence of an axial orthocortex has been observed in straight follicles though less frequently than the abovementioned forms.

The observation that similar patterns of the considered presumptive ortho- and paracortical cells in the bulb, which result in different patterns of ortho- and paracortex in the fibre, may indicate that differential movement of presumptive cells does occur during fibre formation due to differential cell growth in different follicles.

It is suggested that in deflected bulbs, in which the presumptive cells are packed into two segmental cell masses, any cell movement resulting from differential growth will not disrupt the relative position of each segment. In follicles tending to be straight, in which groups of one type of presumptive cell may be surrounded by the other type, differential cell growth may result in a displacement of cell types, relative to each other. This could lead to a variety of ortho- and paracortical patterns in the fibre, the positioning of which may be dependent upon the initial position of the presumptive cells in the bulb, and the cell growth rate differential.

Though the fibre paracortex in deflected follicles is consistently associated with the thin wall of the follicle (Mercer 1954; R. D. B. Fraser and Rogers 1955) the position of the paracortical cells in fibres from follicles tending to be straight are not necessarily so. In Plate 5, Figures 1 and 2, paracortical cells are not adjacent to the thin wall of the follicle, thus paracortex on the thin side of deflected follicles is coincident with bulb deflection, and not formed as a result of being adjacent to the thin wall. The first basophilic response in paracortical cells, using methylene blue, occurs most intensely around the nuclei of such cells (Plate 6, Fig. 2), though some

extrafollicular stimulus may be acting on the already predetermined paracortical cells. Again, all of the fibre cuticle is para in form when the early signs of a basophilic response occurs within the cortex (Plate 6, Fig. 2).

In all follicles studied, whether deflected or tending to be straight, the position of the initial picrophilous reaction of the inner root sheath was consistently associated with the level and position, within the germinative region, at which cellular differentiation commences. As this phenomenon always occurs, it seems possible that the onset of keratinization of the inner root sheath determines the levels in the bulb at which cellular differentiation commences. Differentiation could be affected indirectly in this way by mitotic activation or mitotic inhibition. An activator may be prevented from diffusing into the germinative cells through the keratinized root sheath, or a mitotic inhibitor may be prevented from diffusing out, or the root sheath may release an inhibitor to the cells of the germinative region. If the former be the case, glucose could be considered as a possible mitotic activator. It is clear that the entry of glucose occurs through the outside of the bulb as well as via the papilla (Ryder 1958).

In follicles tending to be straight, in which the inner root sheath begins to differentiate at an even level around the bulb, the fact that mitosis tends to be restricted to around the papilla at its distal limits suggests that entry or disposal of the activator or inhibitor is restricted to via the papilla at such distal papilla sites.

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EXPLANATION OF PLATES 1–6

P, papilla; *MC*, mitotic cells; *DC*, differentiating cells; *IRS*, inner root-sheath; *OC*, orthocortex; PC, paracortex

PLATE 1

Fig. 1.—Median longitudinal section of a deflected wool follicle bulb, showing bilateral cellular and mitotic segmentation. The proximal limits of the inner root sheath on both the ectal and ental side of the bulb deflection are marked.

Fig. 2.—Median longitudinal section of a straight wool follicle bulb showing the localization of mitotic figures on both sides of the papilla. The first signs of inner root sheath formation occurs at the same level on each side of the follicle, as marked.

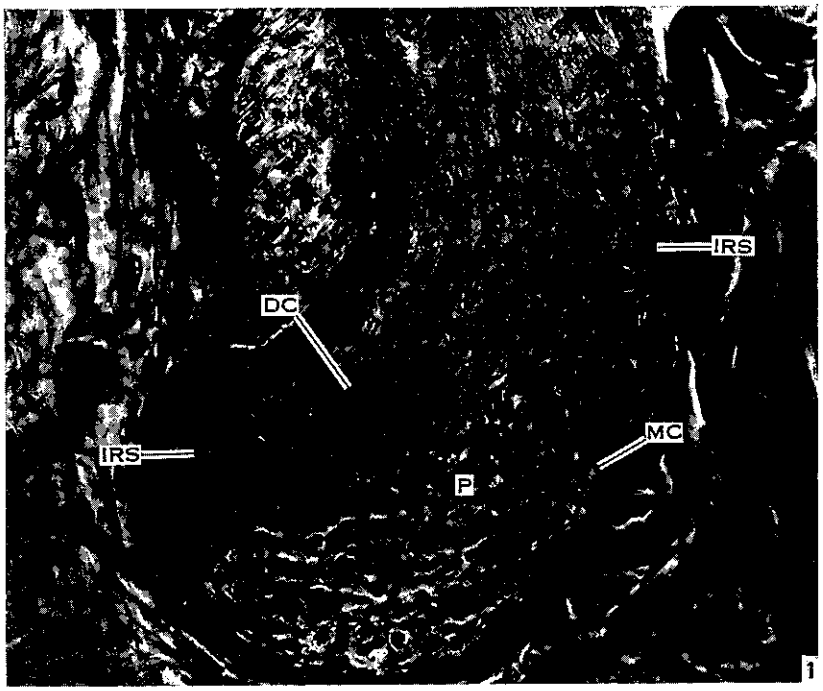
PLATE 2

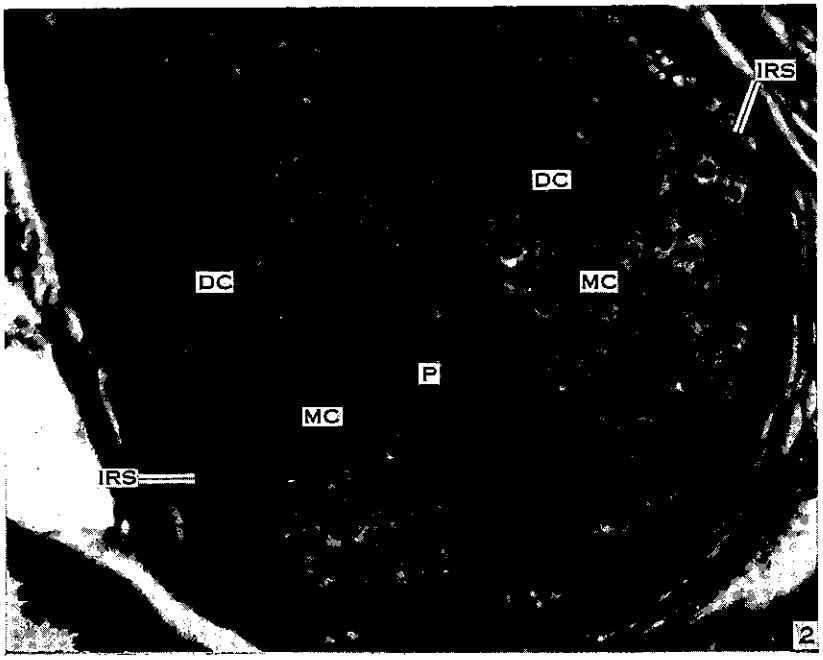
Figs. 1–9.— Alternate transverse sections from a serial sequence, proximodistally, of a deflected follicle bulb.

PLATE 3

Figs. 1–9.—Alternate transverse sections from a serial sequence, proximodistally, of a follicle tending to be straight.

STUDIES ON THE FOLLICLE BULB OF FIBRES. I





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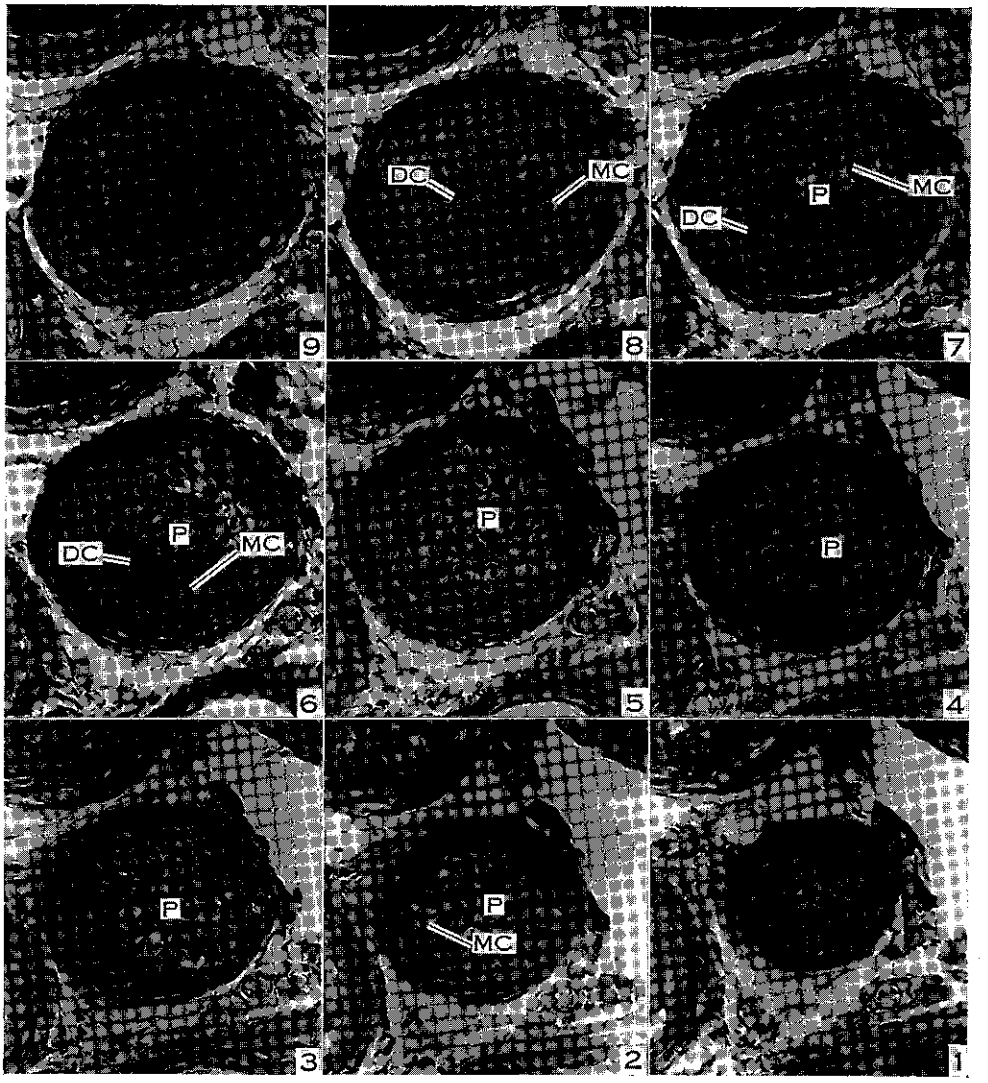

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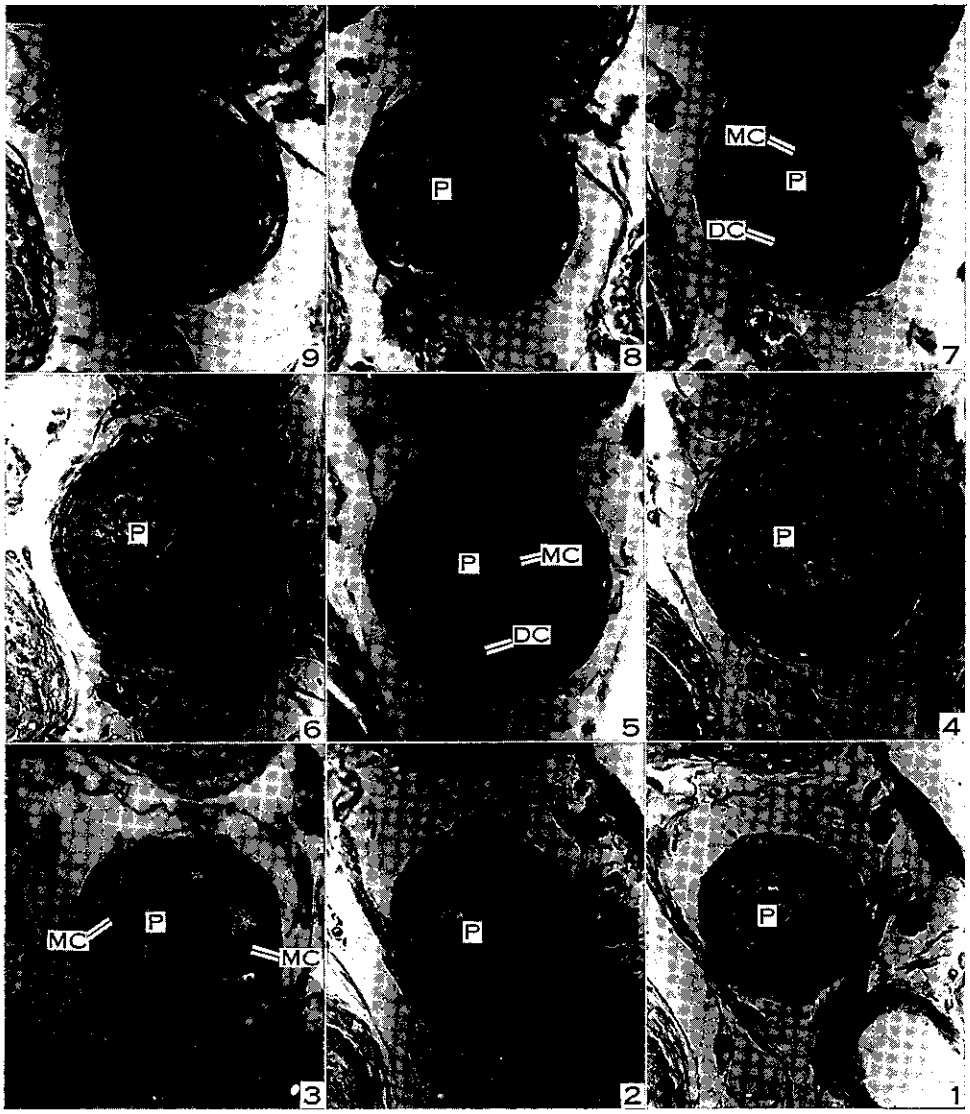

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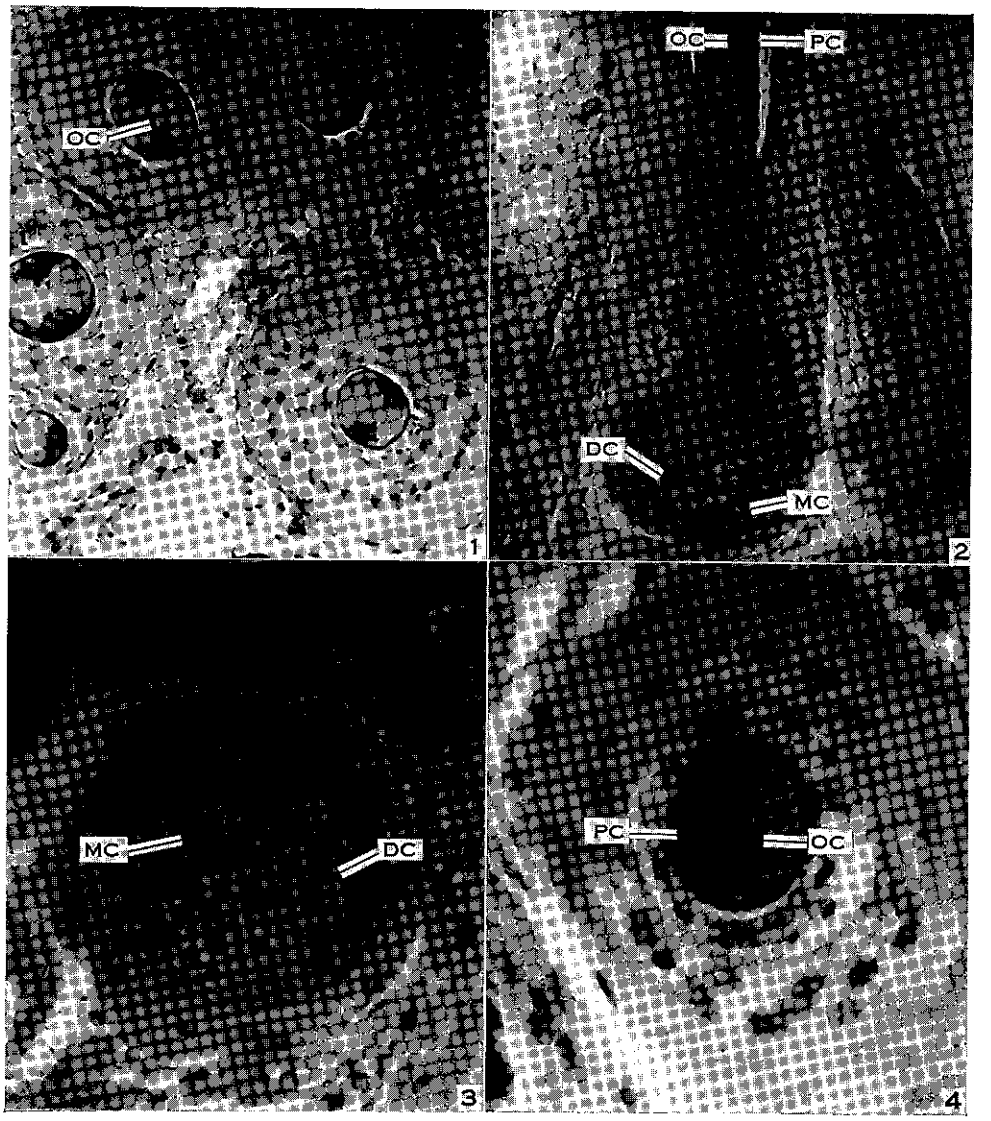
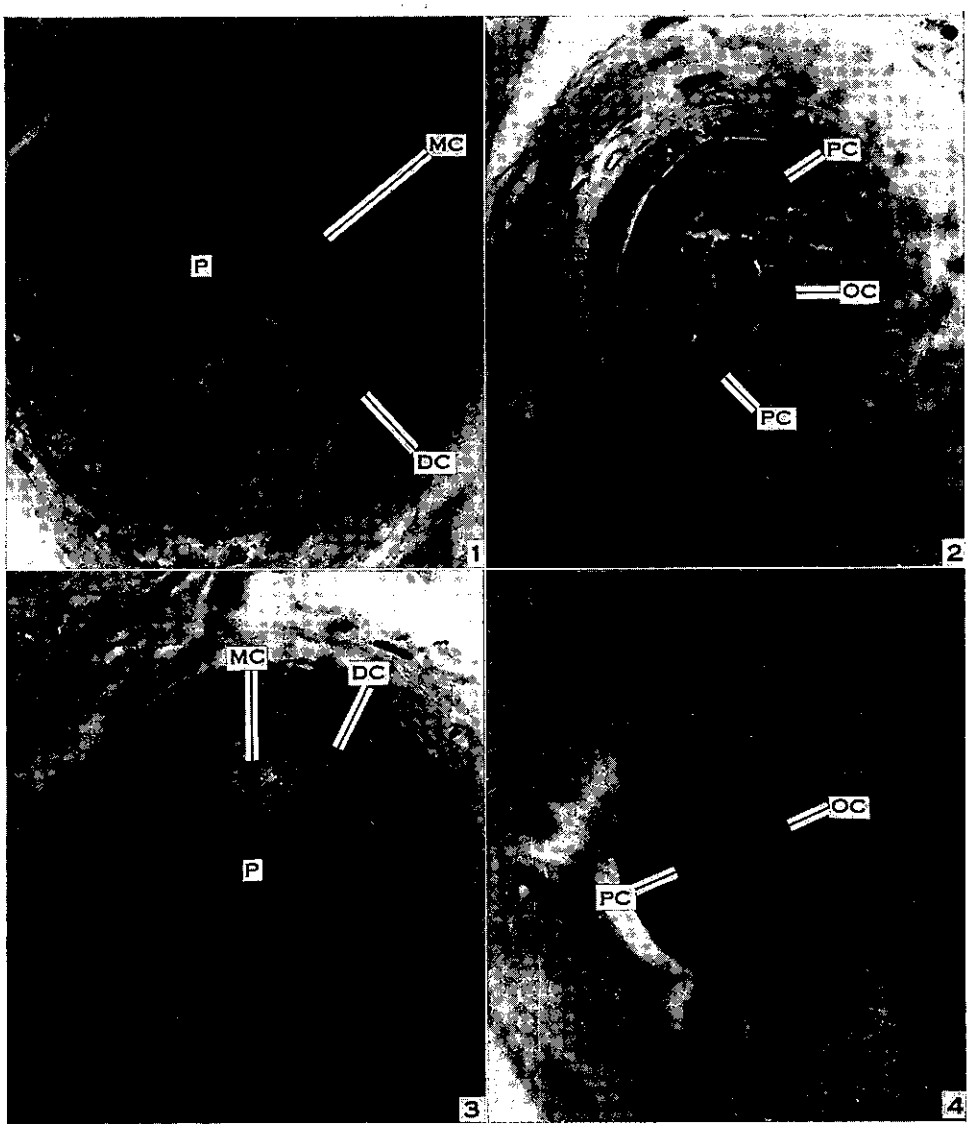
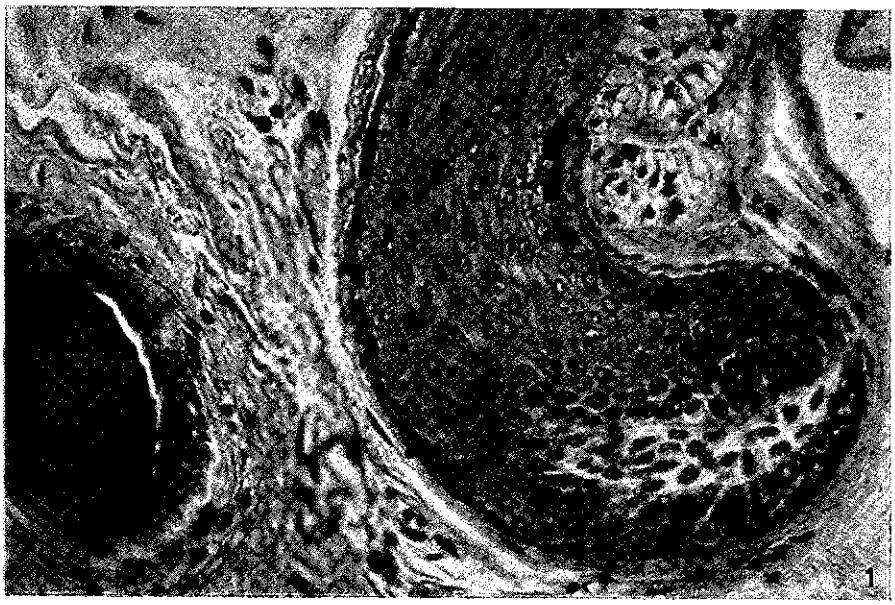


STUDIES ON THE FOLLICLE BULB OF FIBRES. I



STUDIES ON THE FOLLICLE BULB OF FIBRES. I



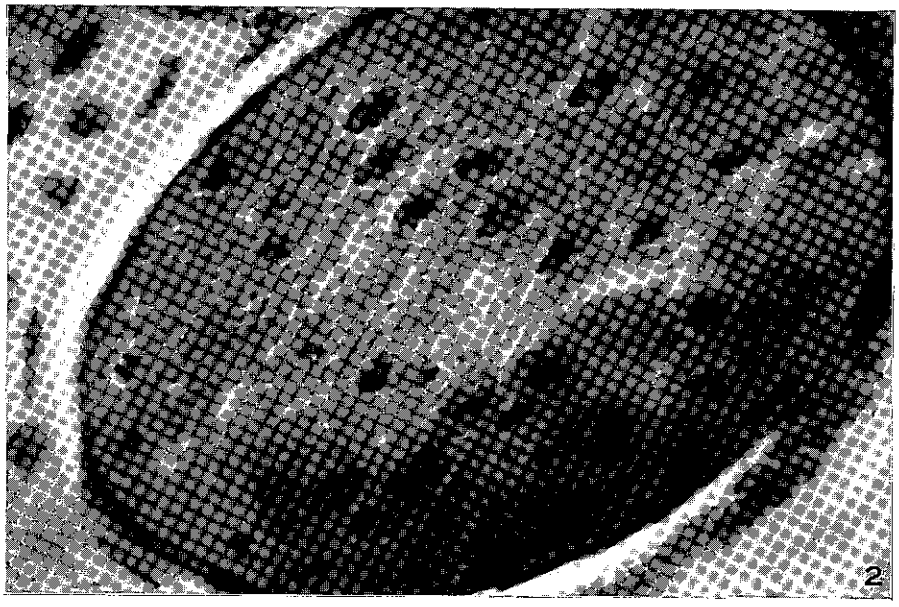


PLATE 4

Fig. 1.—Transverse section of Romney sheep skin showing different types of ortho- and paracortical cell deposition.

Fig. 2.—Median longitudinal section of a follicle from a Romney sheep showing the mitotic and cellular segmentation of the germinative region in relation to the segmentation, ortho and para of the cells of the fibre cortex.

Figs. 3 and 4.—Transverse sections of the same orientation, from the same deflected follicle. Figure 3 is from the distal level of the germinative region showing bilateral mitotic and cellular segmentation. Figure 4 is from a level in the follicle at which ortho- and paracortical segments are clearly defined.

PLATE 5

Figs. 1 and 2.—Transverse sections of the same orientation from the same straight follicle. Figure 1 is from the distal level of the germinative region showing a random arrangement of mitotic cells localized axially around the papilla. Figure 2 is from a level in the same follicle at which ortho- and paracortical fibre cells are differentiated.

Figs. 3 and 4.—Transverse sections of the same orientation from the same straight follicle. Figure 3 is from the distal level of the germinative region, showing a similar arrangement of mitotic figures to the section in Figure 1. Figure 4 is a section showing ortho- and paracortical cells in the same follicle.

PLATE 6

Fig. 1.—Median longitudinal section of a deflected follicle bulb, showing mitotic cell detail in the bulb, and detail of differentiating cells in the bulb and in the follicle shaft.

Fig. 2.—Transverse section of a wool fibre at a level in the follicle at which ortho- and paracortical segmentation is initiated. The basophilic response to methylene blue is most intense around cell nuclei. The fibre cuticle is clearly defined as para in form at such a follicle level.