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The structure of hair and follicles of mice carrying the naked (*N*) gene

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SUMMARY

The hairs and follicles from mice carrying the naked (*N*) gene have been examined using both scanning and transmission electron microscopy in addition to light microscopy. Fibre cuticle cells and occasionally cortical cells were absent from the follicles of *N*/+ mice when the base of the hair was growing. In *N*/*N* follicles there was a frequent lack of both cuticle and cortical cells throughout the growth phase of the follicles. Abnormalities were also observed in the manner in which the synthesized keratin was deposited in the fibres. The possible mode of action of the *N* gene is discussed in the light of these results.

1. INTRODUCTION

The hairs of mice carrying the naked (*N*) gene are affected by varying degrees of fragility. In heterozygous naked (*N*/+) mice, the hairs exhibit little abnormality until near the end of each cycle of growth, at which time most hairs break off just above the skin surface, leaving the skin bare until the eruption of the next hair coat. In homozygous naked (*N*/*N*) mice, few if any hairs erupt during the first hair cycle, although the follicles are active. Some abnormal hairs do erupt during the second and subsequent cycles, but the majority of hairs still do not emerge from the follicles. On most of the body the hair coat is sparse and the erupted hairs rarely reach more than 2–3 mm in length before breaking off near the skin surface. By contrast, erupted hairs on the posterior dorsum are more numerous and grow to a greater length than those on the body (Lebedinsky & Dauvart, 1927; David, 1932).

A light microscopic study (David, 1932) revealed abnormalities in hair follicles which give rise to hair defects in mice carrying the *N* gene. In anagen follicles actively growing hairs in wild type (+/+) mice, seven layers of cells are present: the outer root sheath, Henle's layer, Huxley's layer and cuticle of the inner root sheath, and the cuticle, cortex and medulla of the hair. By contrast, some follicles of *N*/+ mice lack the cuticle layer of the hair after hair growth has been under

way for some time (David, 1932). In some affected $N/+$ hairs, there are also irregularities in the arrangement of medullary and cortical cells. In follicles of N/N mice, David (1932) recorded that Huxley's layer may be poorly keratinized, the inner root sheath cuticle was sometimes absent, the hair cuticle was generally absent and the hair cortex and medulla were reduced in size. On the basis of the absence of birefringence in polarized light, David (1932) also considered that there was 'lack of keratinization' of affected fibres in both $N/+$ and N/N mice.

The present study is a re-examination of hairs and follicles from mice carrying the naked gene using both scanning and transmission electron microscopy in addition to light microscopy. The findings of David (1932) have not only been confirmed in general, but also extended to show that, as well as disturbance of the arrangement of cell layers in follicles, there are abnormalities in the manner in which the synthesized keratins are deposited in the fibres. The possible mode of action of the naked gene is discussed in the light of these results.

2. MATERIALS AND METHODS

(i) *The mouse stock*

The naked stock was formed initially by crossing an inbred naked stock from the Jackson Laboratory, Maine, U.S.A., and a local coloured strain. Subsequently, the stock was maintained by mating $N/+$ sibs of N/N mice which survived to adulthood.

(ii) *Sampling and examination of hair*

Because hairs did not emerge in sufficient numbers to be sampled from the skin of N/N mice until the third or fourth hair cycle, samples of fully grown hair were taken from adult mice of the three genotypes. Hairs were plucked from the mid-side of two $+/+$ females, from the anterior edge of a hair-band (i.e. the oldest hairs in the band) on the mid-sides of two $N/+$ females and one N/N female, and from the rump of this and another N/N female.

Hairs from the $+/+$, $N/+$ and, where possible, the N/N mice were classified into monotrichs, awls, auchenes and zig-zags (Dry, 1926). Hairs of each type were mounted on scanning electron microscope stubs with thin double-sided adhesive tape, sputter-coated with gold and examined in an I.S.I. Super III A scanning electron microscope in the secondary electron mode.

(iii) *Sampling and examination of skin*

In order to examine the structure of follicles during the successive stages of growth of the hair shaft and hair base, samples of skin were taken from one mouse of each genotype at each of two ages during the first hair cycle, *viz.* 7 days and 12 days postnatally. The skin was excised from the flank and mid-dorsum of each mouse and also from the mid-ventrum of the 12 days-old mice under ether anaesthesia.

The flank samples were fixed in Serra's fluid for 6 h, processed into paraffin and sectioned at 10 μm thickness longitudinally to the follicles. The sections were stained either by the Sacpic procedure (Auber, 1950) or with haematoxylin, eosin and picric acid. The widths of the bulbs of ten zig-zag follicles in each mouse were measured by light microscopy, and the mean for each genotype was determined.

The mid-dorsal and mid-ventral samples were cut into strips, *c.* 1 mm wide, in an anterior–posterior direction along the orientation of the hair follicles. The strips were sliced into *c.* 1 mm lengths longitudinally to the follicles and fixed sequentially for 10 min and 5 h at 4 °C in the Peters, Proskauer & Kaiserman-Abramof (1968) two-stage modification of Karnovsky's (1965) glutaraldehyde-paraformaldehyde fixative. The skin pieces were washed overnight in 0·1 M cacodylate buffer (pH 7·4), postfixed in 1% (w/v) osmium tetroxide in 0·1 M cacodylate buffer for 2 h, dehydrated through increasing concentrations of ethanol and epoxy propane, and embedded in Araldite. During embedding the pieces were orientated to permit either transverse or longitudinal sectioning of the follicles. Sections, 1 μm thick, were cut and stained with Azur A-methylene blue. When desired levels in follicles were obtained, ultrathin sections were cut, and after sequential staining with uranyl acetate (Watson, 1958) and lead citrate (Reynolds, 1963) were examined in a Jeol 100 S transmission electron microscope.

3. RESULTS

Hairs plucked from $N/+$ and N/N mice tended to break at the weakest points with the result that parts of the hairs sometimes remained unplucked. Also those hairs most affected by the N gene did not even erupt through the skin. Thus the hair samples plucked from the mutant mice tended to be biased towards those hairs with a more robust structure than the total population of hairs. However, sections of skin examined in the transmission electron microscope contained follicles producing both the stronger and weaker emergent hairs as well as those that did not erupt through the skin.

(i) *Hair Structure*

The hairs plucked from the pelage of the $+/+$ mice and from the hair bands of the $N/+$ mice could be readily classified into monotrichs, awls, auchenes and zig-zags. Identification of the four hair types in the N/N mice was more difficult. In hair samples from the rump of the N/N mice, it was possible to distinguish zig-zags and overhairs, but in samples from the mid-side only overhairs, which were mainly awls (Fraser, 1951), appeared to be present. Hence the comparisons of hairs among the three genotypes have been confined to awls and zig-zags, and in the case of the N/N mice the awls were from the mid-side and rump, whereas the zig-zags were only from the rump.

Plate 1, figs 1–6 illustrate surface features of awls plucked from $+/+$ and $N/+$ mice, and Plate 2, figs 7–15 show a range of abnormalities on awls of N/N mice.

Both $+/+$ and $N/+$ hairs had finely tapered tips with annulate scale patterns (Plate 1, Figs. 1, 4). As the hairs thickened, the exposed edges of the cuticle cells made an irregular mosaic pattern along most of the length of the hairs (Plate 1, figs. 2, 5). Near the base, the hairs decreased in thickness and the cuticle pattern became petal-like. Club-ends had formed on the $+/+$ hairs (Plate 1, fig. 3), but most $N/+$ hairs were fragmented at the base (Plate 1, fig. 6). The tip ends of the N/N hairs were damaged (Plate 2, figs. 7, 10, 13) due to splitting and breaking of the hairs. Relatively intact N/N hairs from the rump had cuticle scale patterns on the shaft (Plate 2, fig. 8). Other malformed N/N hairs from the mid-side either lacked cuticle scale pattern (Plate 2, fig. 11) or had a rough nodular surface (Plate 2, fig. 14). A variety of malformations was present on the root-ends of N/N hairs (Plate 2, figs. 9, 12, 15).

Plate 3, figs. 16–24 illustrate surface features of zig-zag hairs of the three genotypes. Zig-zags from $+/+$ and $N/+$ mice had overlapping cuticle cells along their lengths (Plate 3, figs. 16–18, 19–21) which exhibited changing scale patterns similar to those on $+/+$ awls. However, unlike $+/+$ hairs the tips on $N/+$ zig-zags generally were malformed or broken (Plate 3, fig. 19) and, in the regions between the constrictions, the shafts were sometimes kidney shaped in section rather than being circular. In addition the cuticle cells on the shafts of $N/+$ hairs were occasionally malformed with gaps between them (Plate 3, fig. 20). At the base of the $N/+$ zig-zags the cuticle cells had a roughened, nodular surface (Plate 3, fig. 21), similar to that on the shafts of N/N awls (Plate 2, fig. 14). Zig-zags from N/N mice generally had malformed and broken tips from which cuticle cells were missing (Plate 3, fig. 22). Just below the tips cuticle cells were present, but exhibited little overlapping and no scale pattern (Plate 3, fig. 22). The cuticle cells on the shafts of N/N zig-zags had slightly roughened surfaces and overlapped to produce a mosaic pattern (Plate 3, fig. 23). By contrast, at the base of N/N zig-zags there was little overlapping of cuticle cells (Plate 3, fig. 24).

(ii) *Follicle Structure*

The mean width of the follicle bulbs in the 12 days-old N/N mouse ($\bar{x} = 40{\cdot}4 \pm 3{\cdot}8$ μm) was smaller than that of the bulbs in the 12 days-old $+/+$ and $N/+$ mice ($\bar{x} = 53{\cdot}6 \pm 6{\cdot}3$ μm and $49{\cdot}2 \pm 3{\cdot}0$ μm respectively).

Ultrastructural comparisons of follicles between genotypes were confined in the main to zig-zag follicles. In the 7 days-old $+/+$ mouse, which at this age was growing the shaft region of the hairs, the arrangement of the cell layers in the follicles was normal (Plate 4, fig. 25). The outer root sheath cells, which contained accumulations of glycogen (Plate 4, fig. 25, insert *a*), surrounded the three layers of inner root sheath cells – Henle's layer, Huxley's layer and inner root sheath cuticle. Prior to the hardening of these layers the cells contained characteristic trichohyalin granules (Plate 4, fig. 25). The hair within the inner root sheath consisted of the hair cuticle (usually one cell thick, except at overlaps of cells) around an annulus of cortical cells, within which was a core of medullary cells. In

the hair cuticle cells dense aggregates accumulated adjacent to the cell membrane in juxtaposition to the inner root sheath cuticle (Plate 4, fig. 25, inset *b*), which is the site of the exocuticle. Within the cortical cells the synthesized keratin proteins formed macrofibrils, consisting of a microfibril-matrix complex (Plate 4, fig. 25, inset *c*). The medullary cells contained granules (Plate 4, fig. 25, inset *d*) and became progressively vacuolated before they hardened. Pigment granules were present in the cortical and medullary cells, but not in the hair cuticle or inner root sheath cells (Plate 4, fig. 25).

Follicles growing the shaft region of hairs in the 7 days-old $N/+$ mouse were generally normal (Plate 5, fig. 26), although in some cortical cells the deposition of the microfibrils and matrix in the developing macrofibrils was somewhat irregular (Plate 5, fig. 26, inset). Follicles in the 7 days-old N/N mouse were grossly abnormal in that they were often markedly deficient in hair cuticle and cortical cells (Plate 6, fig. 27), and inner root sheath cells were then adjacent to cortical and medullary cells. When cortical cells were present, macrofibril formation appeared to be retarded in them (Plate 6, fig. 27, inset *a*). When cuticle cells were present they sometimes contained abnormal globular deposits, which were not pigment granules (Plate 6, fig. 27, inset *b*). Pigment granules were present in fibre and medullary cells, as in $+/+$ and $N/+$ hairs, but on occasions were also abnormally in cuticle cells of the inner root sheath (Plate 6, fig. 27).

At 12 days of age, when the basal portion of hairs was being formed, the arrangement of cell layers in $+/+$ follicles was the same as when the hair shaft was grown (Plate 7, fig. 28). The development of the proteinaceous aggregates in the various cell types was similar to that in follicles of the 7 days-old $+/+$ mouse. In the 12 days-old $N/+$ mouse the cuticle cells of the fibres were often absent, in which case inner root sheath cells were in juxtaposition to cortical cells (Plate 8, fig. 29). In sections of some $N/+$ follicles, both the cortical and cuticle layers of the fibre were often incomplete (Plate 9, fig. 30). Follicles of the 12 days-old N/N mouse exhibited similarly incomplete cuticle and cortical layers of the hairs (Plate 10, fig. 31) as in $N/+$ follicles, while in some follicles the cortical and cuticle cells were absent (Plate 11, fig. 32). In N/N follicles, some cells in positions normally occupied by cuticle cells contained either mainly globular aggregates (Plate 10, fig. 31, inset *a*) or a mixture of globular aggregates and macrofibrils with a microfibril-matrix substructure (Plate 10, fig. 31, inset *b*).

By comparison with follicles in the $+/+$ and $N/+$ mice, the outer root sheaths of the distal parts of many follicles in both the 7 days-old and 12 days-old N/N mice were thickened (hyperplastic) (Plate 12, fig. 33). Within these hyperplastic outer root sheaths, there was not only degradation of the inner root sheaths but also degradation and distortion of the hairs (Plate 12, figs. 33, 34). This resulted in the accumulation of pigment granules and hair remnants in the follicle lumen but no emergent hair.

4. DISCUSSION

The observations in this study confirm David's (1932) findings of the absence of fibre cuticle cells and occasionally of cortical cells in some $N/+$ follicles when the base of the hair is growing, and of a frequent lack of both cuticle and cortical cells in N/N hairs along their length. Because of this deficiency of cuticle and/or cortical cells, the inner root sheath is brought into contact with medulla and cortex in the mutant follicles, and pigment granules are sometimes deposited in the inner root sheath. This latter feature has not been observed in normal follicles.

The inner root sheath and medulla appear to be relatively unaffected by the N gene in our mice. Thus impaired keratinization of Huxley's layer and the occasional lack of cuticle cells of the inner root sheath in N/N follicles, reported by David (1932), were not observed in the present study. Other instances in which the formation of the hair is impaired more than that of the inner root sheath have been reported in lambs on an artificial milk diet (Chapman & Black, 1981) and in regenerating follicles of hairless mice (David, 1932). When dermal papillae from rat vibrissae are recombined with heterotypic epidermis (Oliver, 1970) the inner root sheath is enlarged at the expense of the hair. However in none of these cases is the tubular arrangement of the cuticle and cortex disturbed such that inner root sheath is brought into contact with cortex or medulla.

The paucity of hair erupted through the skin of N/N mice is due largely to degradation of the fibres in the thickened outer root sheaths at the neck of the follicles. The process which normally degrades the inner root sheath in this part of the follicle may also attack the poorly formed fibre. The hyperplastic nature of the outer root sheath at the follicle neck appears to be induced by distortion of the poorly keratinized hair. This effect is also seen in wool follicles when sheep are given diets resulting in the growth of weakened wool (Chapman & Reis, 1978; Chapman & Black, 1981).

Intermittent lack of cuticle and cortical cells, which introduces discontinuities in the tubular arrangement of the cuticle and cortex, may be largely responsible for the fragility of $N/+$ hairs near the base and of N/N hairs along their length. This weakening effect would be even greater in regions of N/N fibres consisting only of medullary cells. In addition, the hairs of $N/+$ mice contain reduced amounts of particular proteins with high proportions of tryrosine and glycine, the high-tyrosine proteins (Tenenhouse & Gold, 1976), which are thought to comprise part of, and help stabilize, the matrix between the microfibrils in the hair cortex (Fraser, Gillespie & MacRae, 1973; Bendit & Gillespie, 1978). Hence the reduced amount of these proteins may contribute in some degree to the fragility of $N/+$ hairs and presumably also of N/N hairs.

There is some debate as to the extent to which a decrease in the content of high-tyrosine proteins in fibres is correlated with loss of strength. Weakness has been reported in wool with reduced amounts of these proteins following the treatment of sheep with certain dietary supplements or various depilating agents (Frenkel, Gillespie & Reis, 1974; 1975). By contrast, the early regrowth of wool

fibres regenerating after plucking and the tips of fibres of lambs and young mice, which are stated without measurement to have normal strengths, also have reduced contents of high-tyrosine proteins (Gillespie, Frenkel & Reis, 1980).

Whether the irregular deposition of matrix in developing macrofibrils of $N/+$ hairs is an expression of impaired synthesis of the high-tyrosine proteins is unknown. The mixture of globular deposits and macrofibrils observed in cells of N/N hairs adjacent to the inner root sheath when there was no clearly defined cuticle cell may represent the synthesis of both cuticle and cortical proteins within the one cell. This would suggest that the position of the cell within the follicle and its neighbouring cells influence the type of protein synthesised. The large globular deposits seen in some 'cuticle' cells probably produced the nodular excrescences seen on the surface of the N/N hairs.

The effect of the N gene appears to be two-fold, first affecting the number and type of cells entering the hair, and secondly, impairing the subsequent synthesis of the high-tyrosine proteins and the manner in which the synthesized keratin proteins are deposited in the fibre cells. The site of action of the N gene is in the epithelial component of the follicle (Raphael & Pennycuik, 1980). More specifically, since bulb sizes are smaller in the N/N mouse, the N gene acts in the mitotically active region of the follicle bulb thereby reducing the total cell population. There is evidence from wool follicles that cell type is determined in the follicle bulb (Chapman & Gemmell, 1971), and in non-medullated wool fibres less than 20% of bulb cells enter the hair cortex (Short, Wilson & Schinckel, 1965; Wilson & Short, 1979). If the cell kinetics in mouse and sheep follicles are similar, a relatively small reduction in the total cell population of the follicle bulb, if confined mainly to presumptive hair cells, would have a large effect on the hair itself. Seemingly in the case of the N gene there is a greater effect on the cuticle and cortex than on the medulla. The velvet mutation is closely linked to N on chromosome 15 of the mouse (Stieler & Hollander, 1972) and, like N, causes fragility of hair in heterozygotes. Homozygous velvet embryos die *in utero* and it is the differentiation and growth of the ectoderm that is affected (Granholm, Stevens & Theiler, 1979). It would seem reasonable, therefore, to postulate that the chromosomal region containing the naked and velvet genes is involved in controlling the proliferation and differentiation of epithelial cells.

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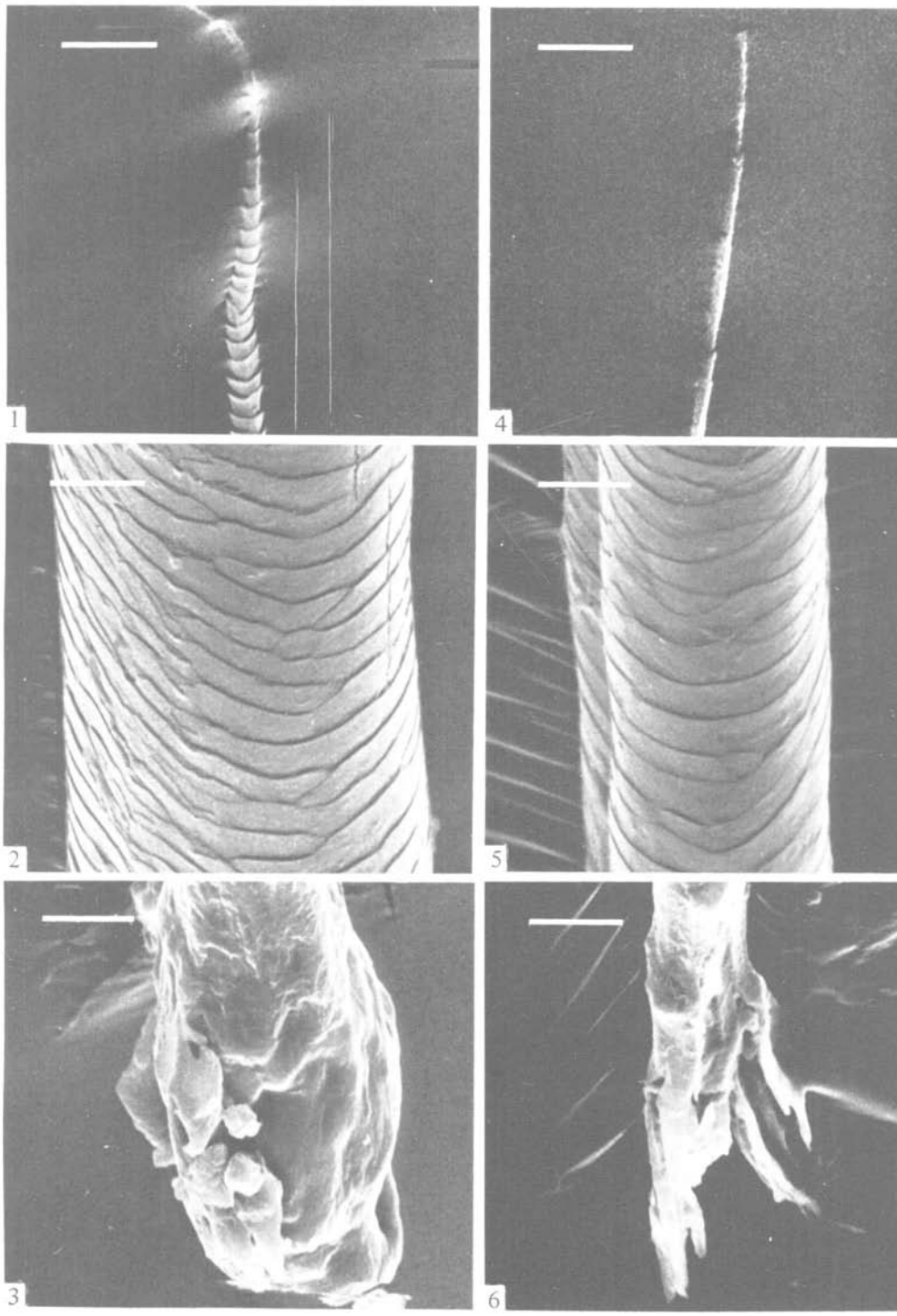
EXPLANATION OF PLATES

PLATE 1

Figs. 1–6. The surface features of the tips, shafts and bases of awls plucked from the mid-sides of the adult +/+ (Figs. 1–3) and *N*/+ mice (Figs. 4–6). The features are normal except for the fragmented base of the *N*/+ awl (Fig. 6). Bar-lines = 10 μm.

PLATE 2

Figs. 7–15. The tips, shafts and bases of three awls (Figs. 7–9, 10–12, 13–15) plucked from the mid-side and rump of the adult *N*/*N* mouse, showing a variety of abnormalities. Bar-lines = 10 μm.



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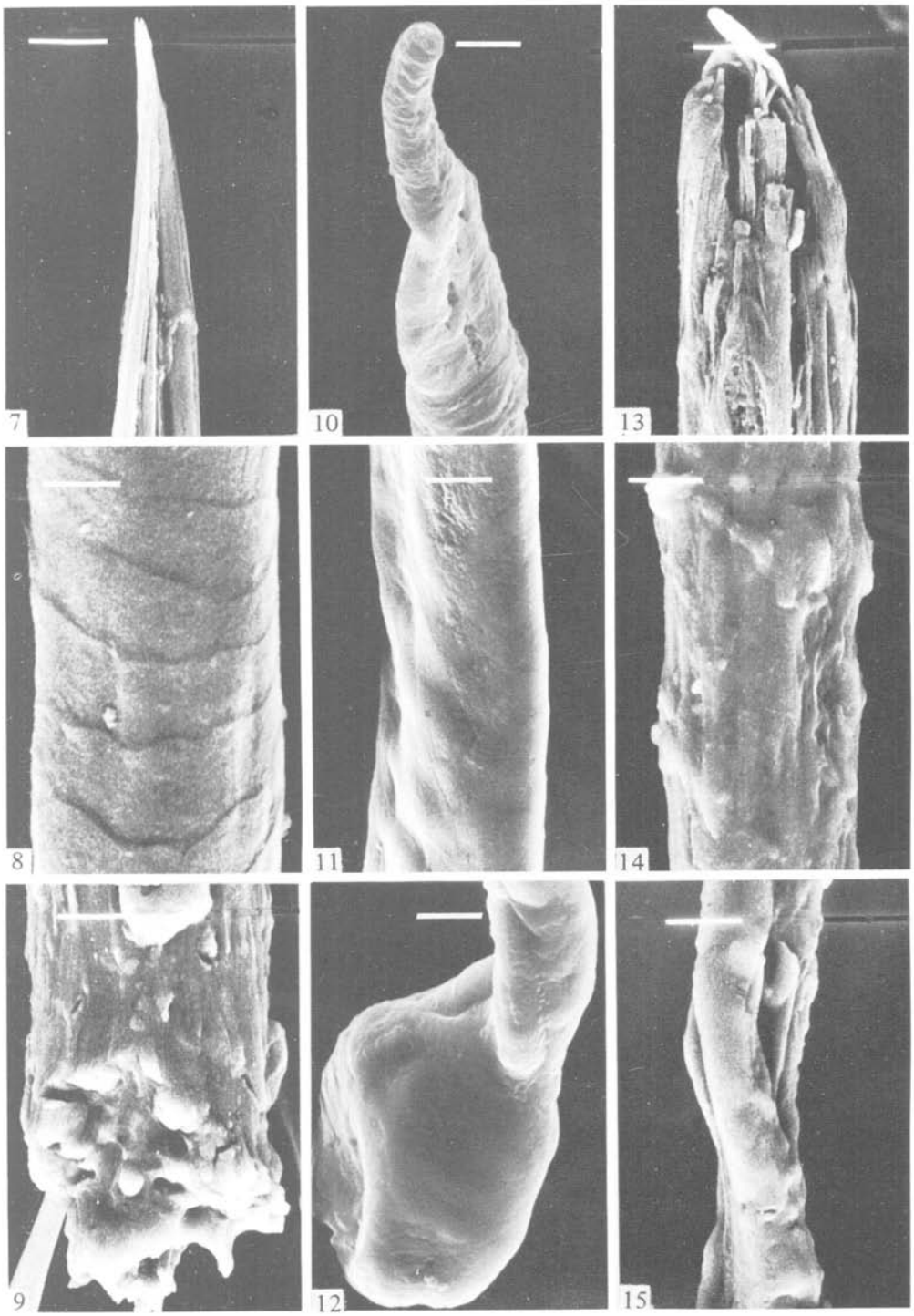

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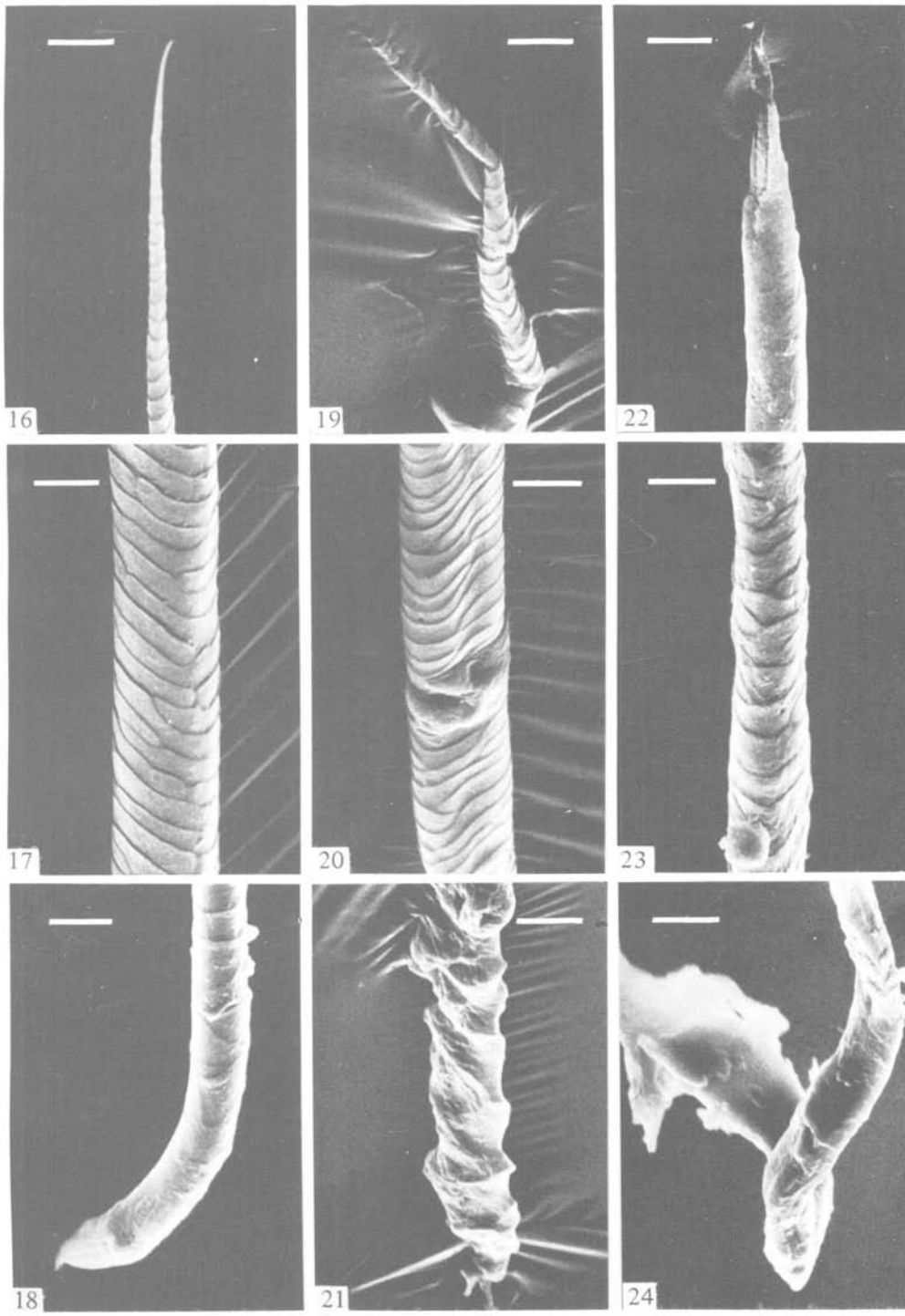

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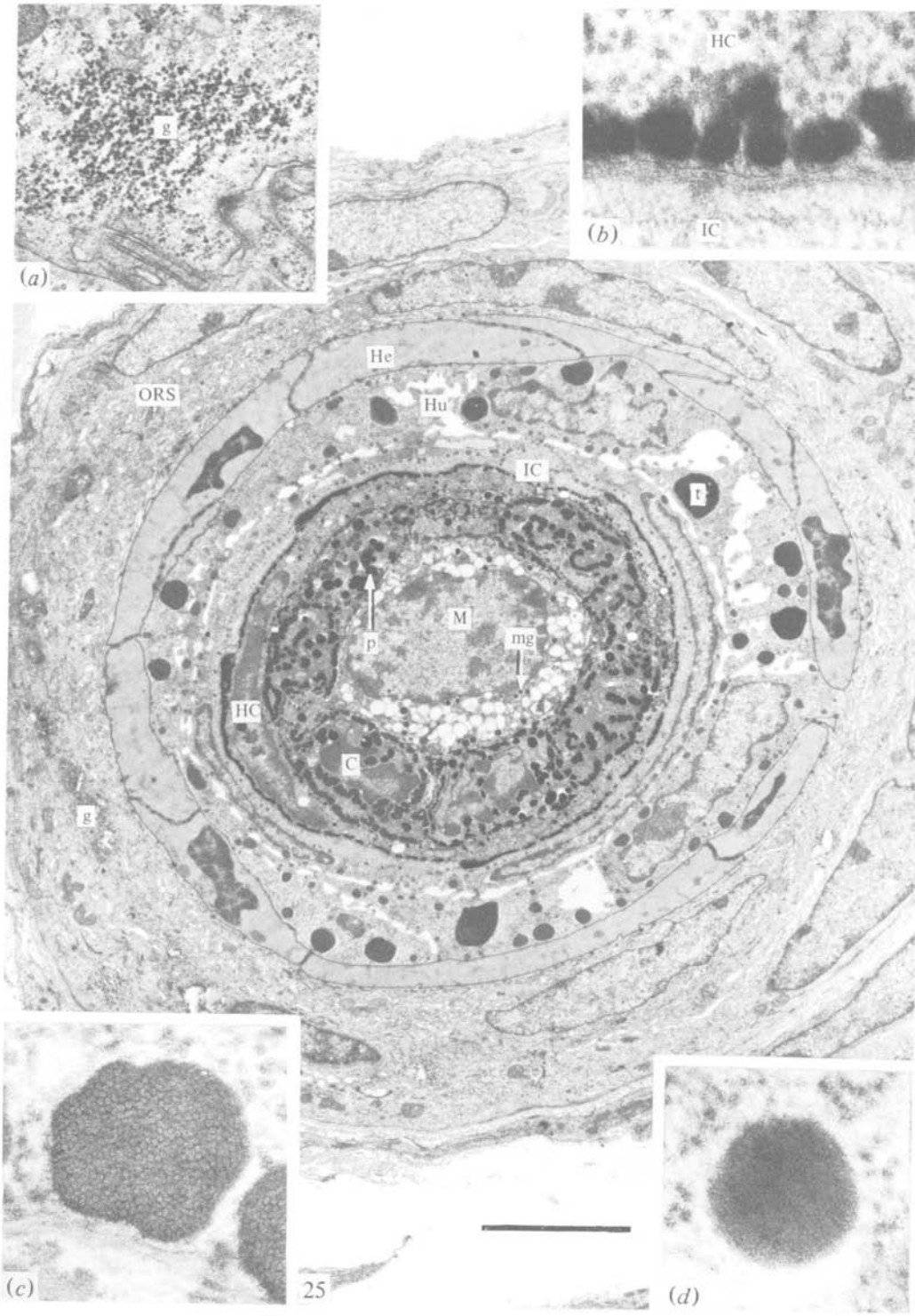

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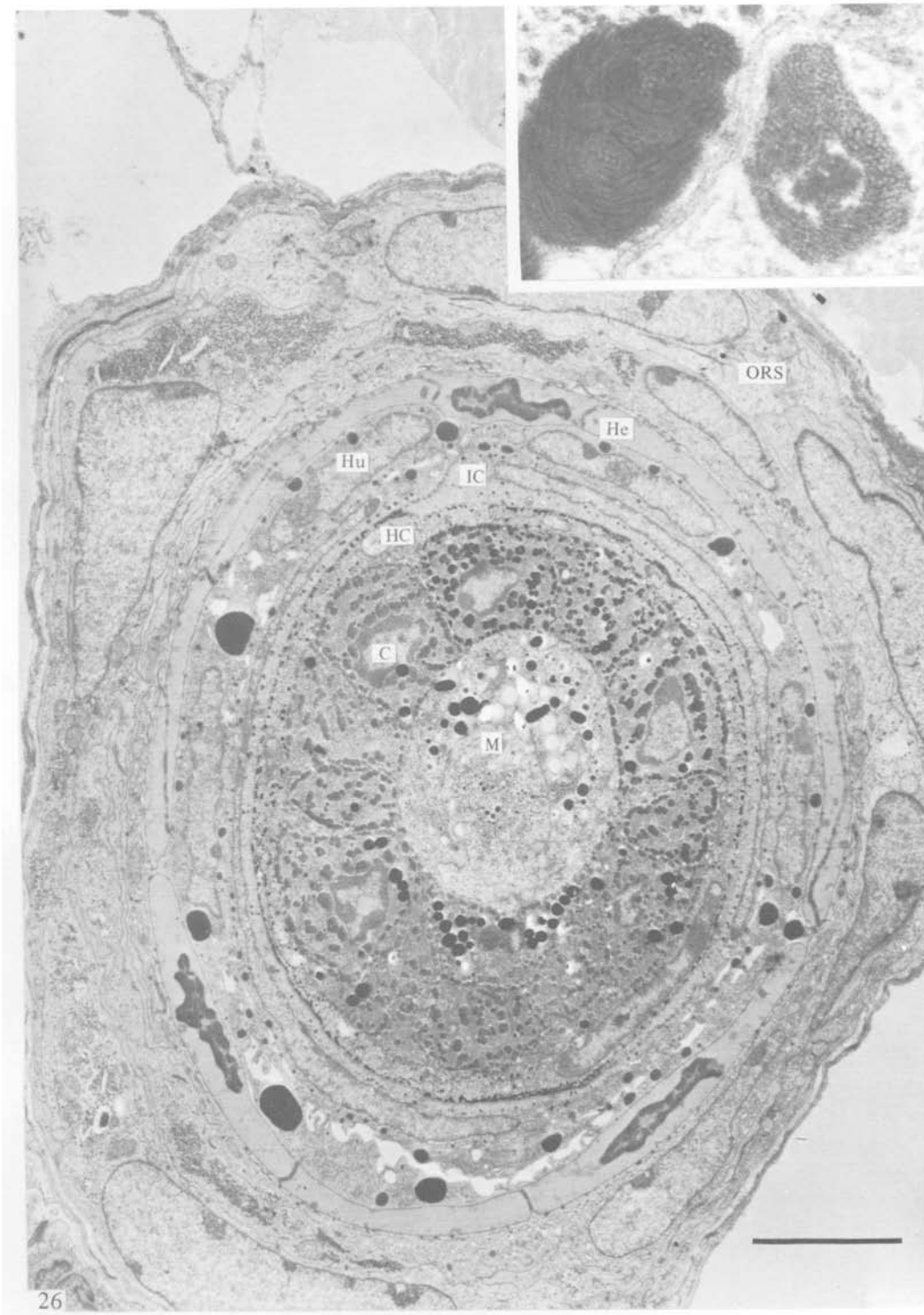

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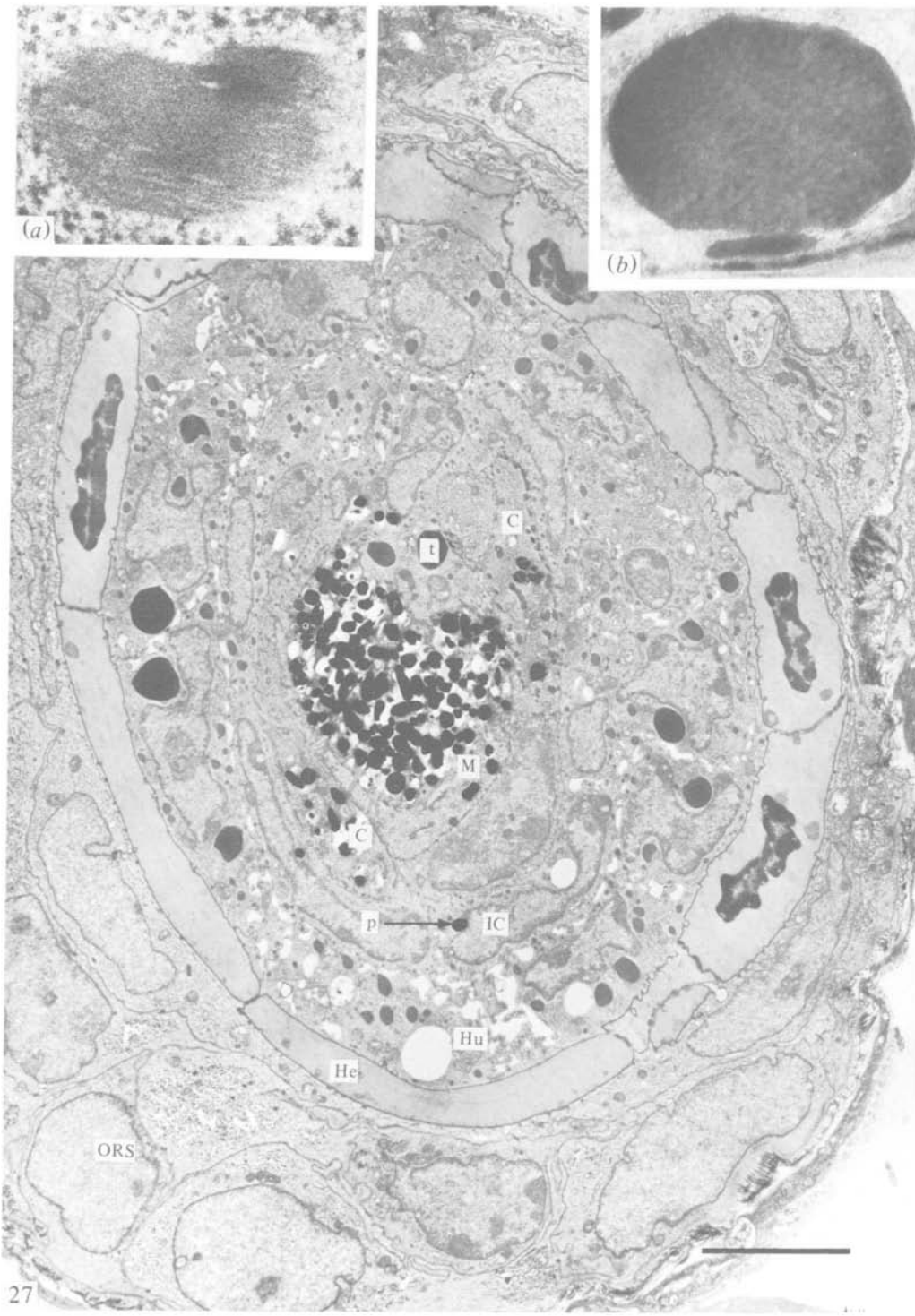

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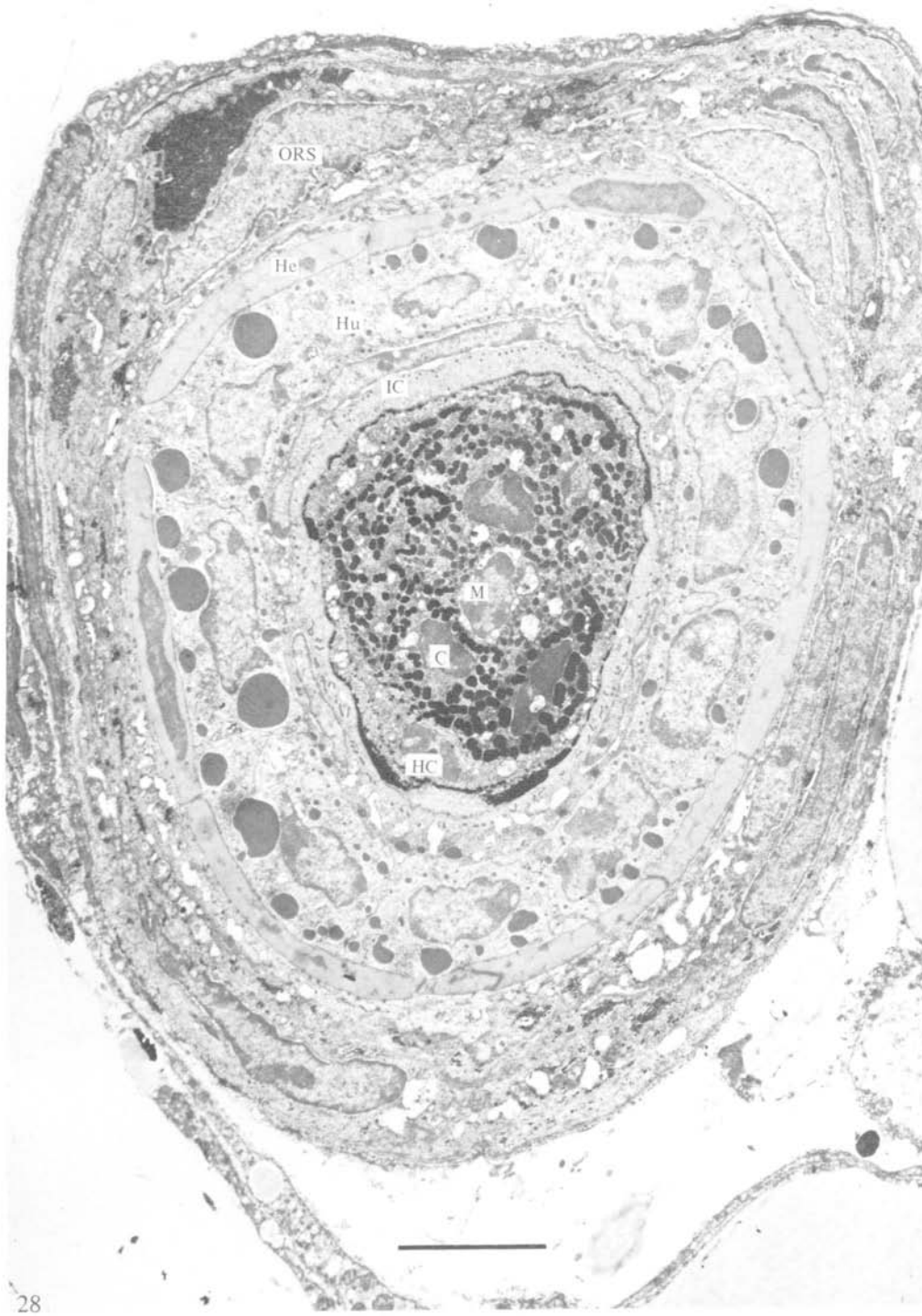

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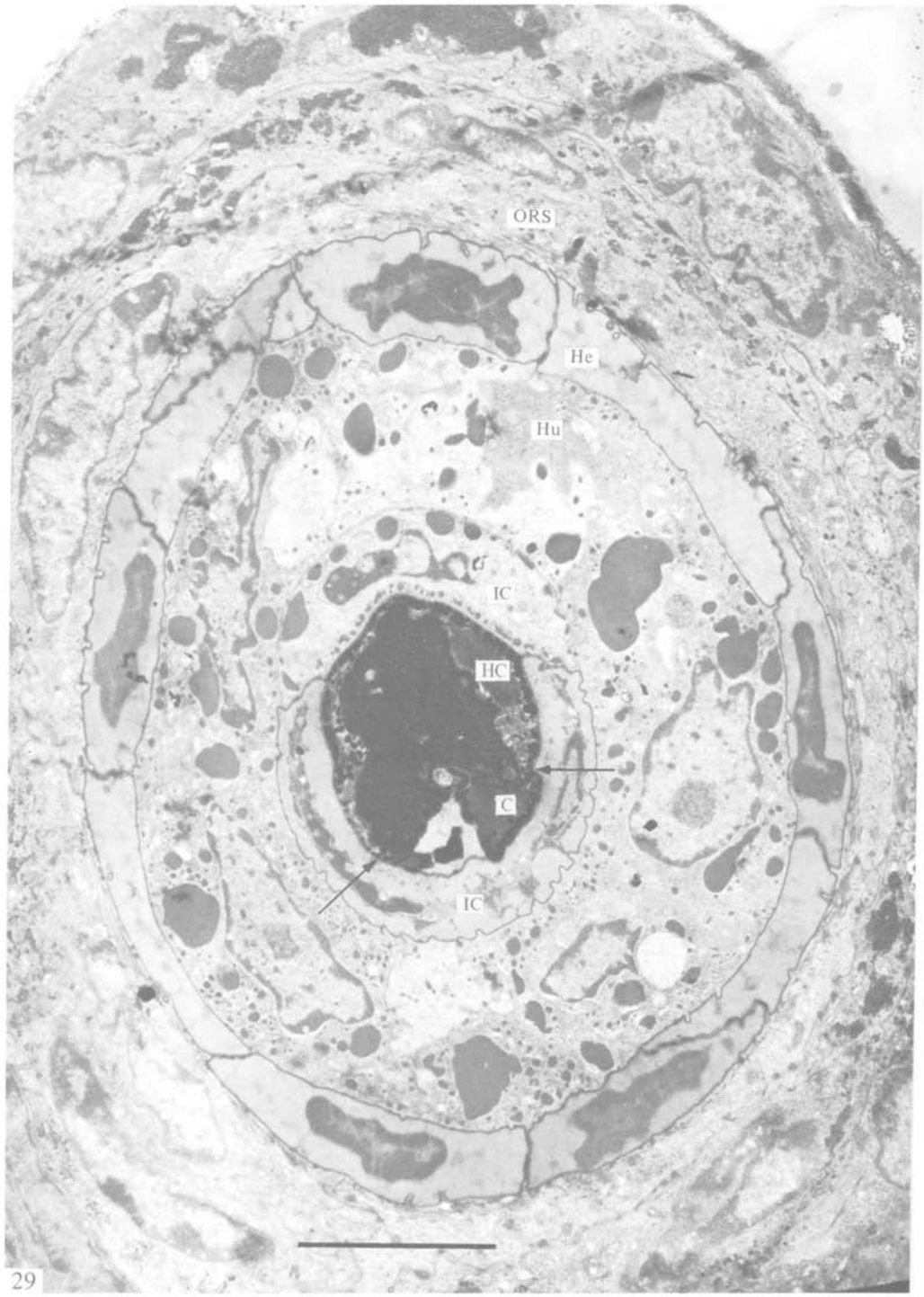

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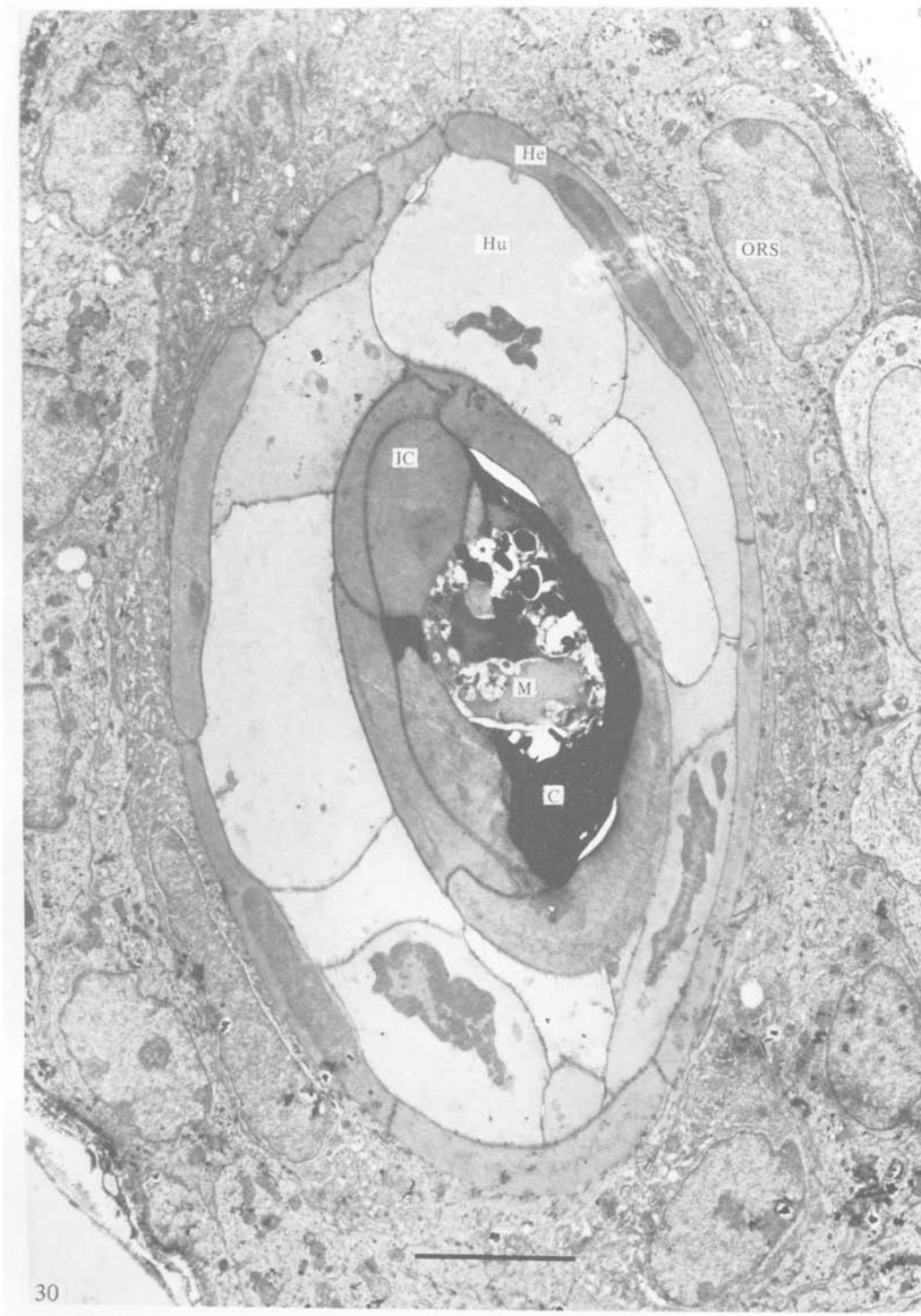

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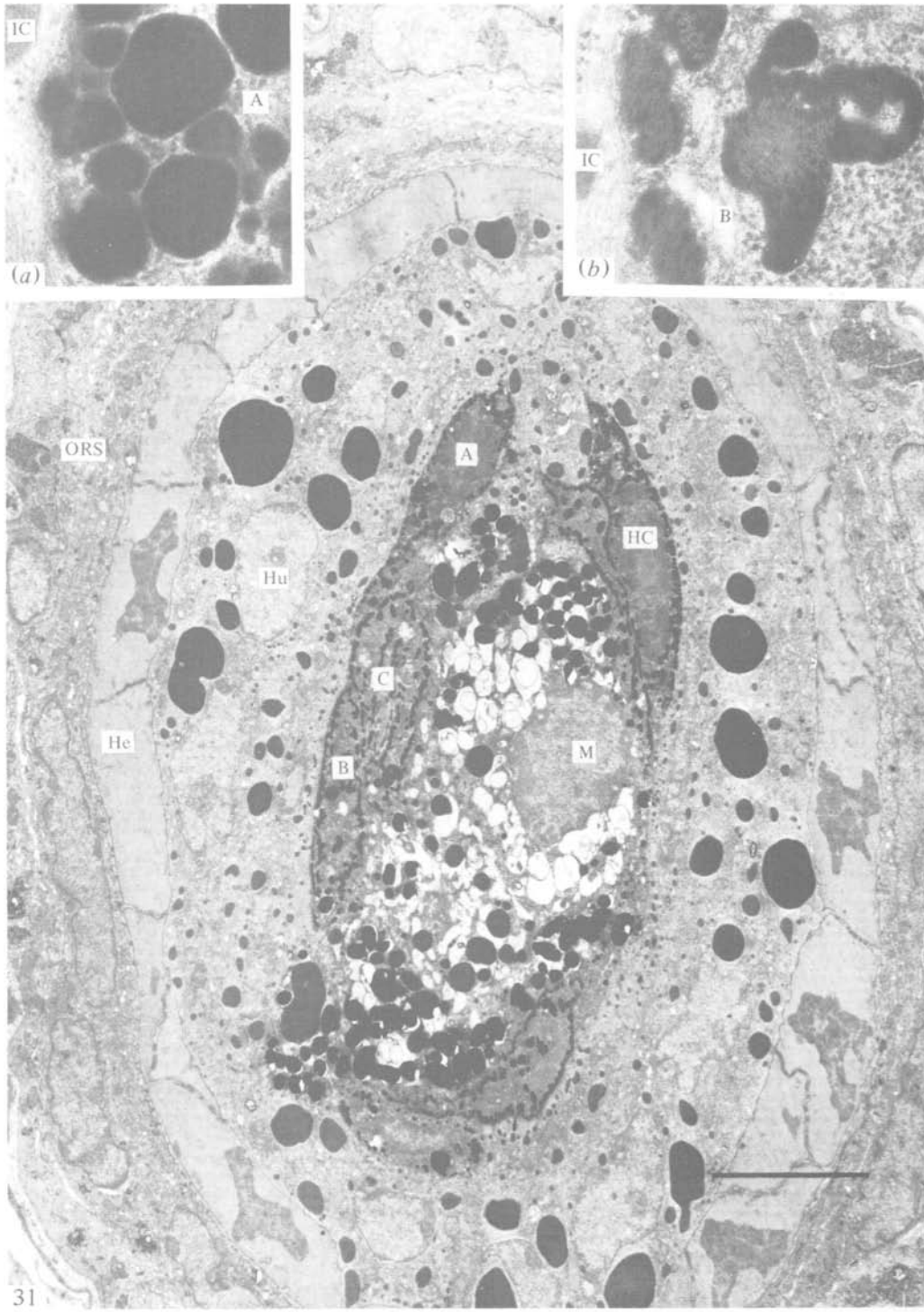

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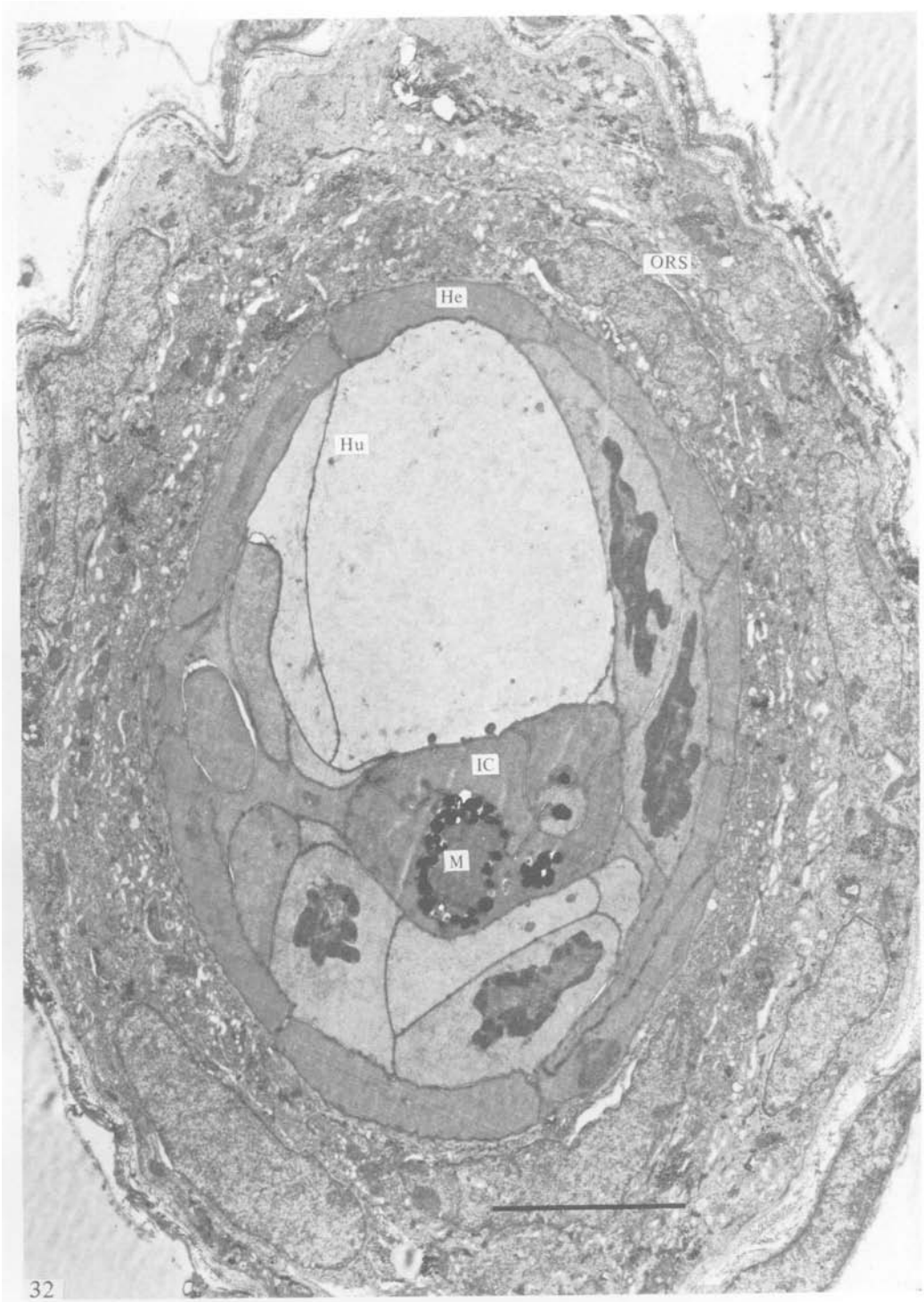

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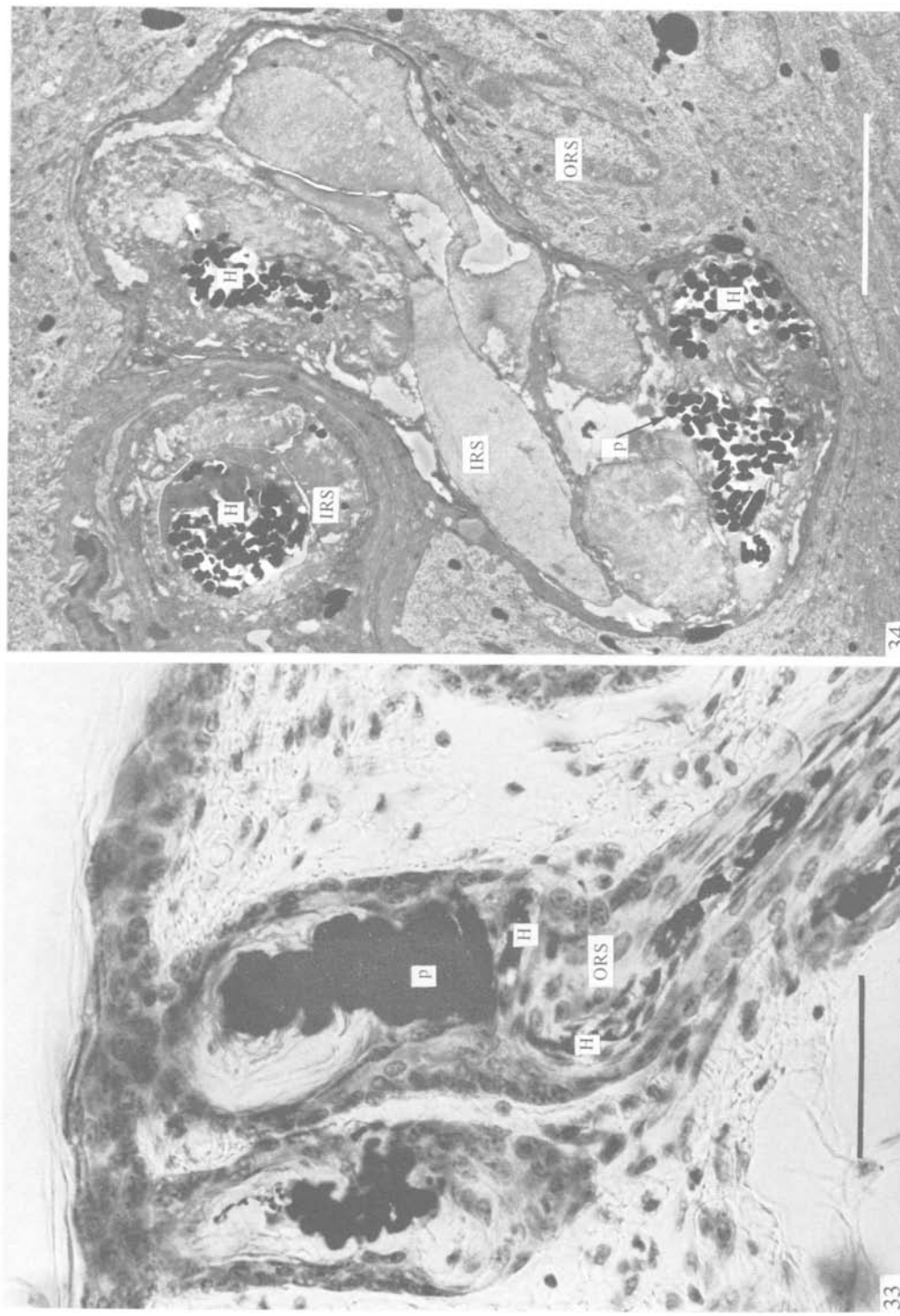

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PLATE 3

Figs. 16–24. The surface features of the tips, shafts and bases of zig-zag hairs plucked from the +/+ (Figs. 16–18), *N*/+ (Figs. 19–21) and *N*/*N* mice (Figs. 22–24). Abnormalities were present along the *N*/+ and *N*/*N* hairs. Bar-lines = 10 μm.

PLATE 4

Fig. 25. Transverse section of a follicle from the 7-day-old +/+ mouse at the level where Henle's layer (He) of the inner root sheath has hardened. Inset (*a*), glycogen (g) in the outer root sheath (ORS). Inset (*b*), dense aggregates in the hair cuticle (HC). Inset (*c*), macrofibril, consisting of a microfibril-matrix complex in the cortex (C). Inset (*d*), granule (mg) in the medulla (M). t, trichohyalin granule in Huxley's layer (Hu) of the inner root sheath; p, pigment granule in the cortex; IC, inner root sheath cuticle. Bar-line = 5 μm main figure, 1 μm inset (*a*), 0·2 μm insets (*b*), (*c*) and (*d*).

PLATE 5

Fig. 26. Transverse section of a follicle from the 7-day-old *N*/+ mouse at the level where Henle's layer (He) of the inner root sheath has hardened. Inset, macrofibrils in the cortex (C) with irregular deposition of microfibrils and matrix on the right. ORS, outer root sheath; Hu, Huxley's layer; IC, inner root sheath cuticle; HC, hair cuticle; M, medulla. Bar line = 5 μm main figure, 0·2 μm inset.

PLATE 6

Fig. 27. Transverse section of a follicle from the 7-day-old *N*/*N* mouse at the level where Henle's layer (He) of the inner root sheath has hardened. Note the deficiency of hair cuticle and cortical cells.

Hair cuticle cells could not be positively identified due to the absence of dense aggregates characteristic of these cells (see Fig. 25). Two cortical cells (C) contain macrofibrils, one of which is shown in inset (*a*). The microfibril-matrix complex is indistinct in these macrofibrils. Inset (*b*), an abnormal globular deposit in a hair cuticle cell (from a different follicle to that shown in this figure). t, trichohyalin granule in an inner root sheath cell which is adjacent to the medulla (M) and a cortical cell (C). p, pigment granule in an inner root sheath cuticle (IC) cell. ORS outer root sheath; Hu, Huxley's layer. Bar-line = 5 μm main figure, 0·25 μm inset (*a*), 0·3 μm inset (*b*).

PLATE 7

Fig. 28. Transverse section of a follicle from the 12-day-old +/+ mouse at the level where Henle's layer (He) has hardened. The medulla (M) is smaller towards the base of the hair. ORS, outer root sheath; Hu, Huxley's layer of the inner root sheath; IC, inner root sheath cuticle; HC, hair cuticle; C, cortex. Bar-line = 5 μm.

PLATE 8

Fig. 29. Transverse section of a follicle from the 12-day-old *N*/+ mouse at the level where Henle's layer (He) has hardened and the inner root sheath cuticle (IC) has almost hardened. This follicle is producing the portion of hair with no medulla just above the hair club. Note the lack of hair cuticle (HC) in the lower portion of the section, between the two arrows, and the position of inner root sheath cuticle next to the cortex (C) in this region. ORS, outer root sheath; Hu, Huxley's layer. Bar-line = 5 μm.

PLATE 9

Fig. 30. Transverse section of a follicle from the 12-day-old *N*/+ mouse at the level where Henle's layer (He), Huxley's layer (Hu) and the inner root sheath cuticle (IC) have hardened. Note the absence of hair cuticle and the incomplete cortex (C). The inner root sheath cuticle is in juxtaposition to cortical cells and medulla (M). ORS, outer root sheath. Bar-line = 5 μm.

PLATE 10

Fig. 31. Transverse section of a follicle from the 12-day-old N/N mouse at the level where Henle's layer (He) of the inner root sheath has hardened. The hair cuticle (HC) and the cortex (C) are incomplete. The cell marked A contains large globular aggregates, enlarged in inset (*a*). The cell marked B contains a mixture of globular aggregates and macrofibrils with a microfibril-matrix substructure, enlarged in inset (*b*). ORS, outer root sheath; Hu, Huxley's layer; IC, inner root sheath cuticle; M, medulla. Bar-line = 5 μm main figure, 0·4 μm insets (*a*) and (*b*).

PLATE 11

Fig. 32. Transverse section of a follicle from the 12-day-old N/N mouse at the level where Henle's layer (He), Huxley's layer (Hu) and the inner root sheath cuticle (IC) have hardened. There is no hair cuticle or cortex. The cell labelled M is either a hardened medullary cell or a continuation of the inner root sheath cuticle. ORS, outer root sheath. Bar-line = 5 μm.

PLATE 12

Fig. 33. Longitudinal section of the distal part of a follicle of the 12-day-old N/N mouse, in which the hair (H) is distorted and degraded within a thickened portion of the outer root sheath (ORS). Pigment granules (P) accumulate in the lumen of the follicle, but no fibre emerges. Bar-line = 50 μm.

Fig. 34. Cross-section of distorted portions of a hair (H) degraded and releasing pigment granules (P) in the distal part of a follicle in the 7-day-old N/N mouse. This is at a level where the inner root sheath (IRS) is undergoing degradation, but has not sloughed into the follicle lumen. ORS = outer root sheath. Bar-line = 5 μm.