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The expression of the gene *asebia* in the laboratory mouse

2. Hair follicles

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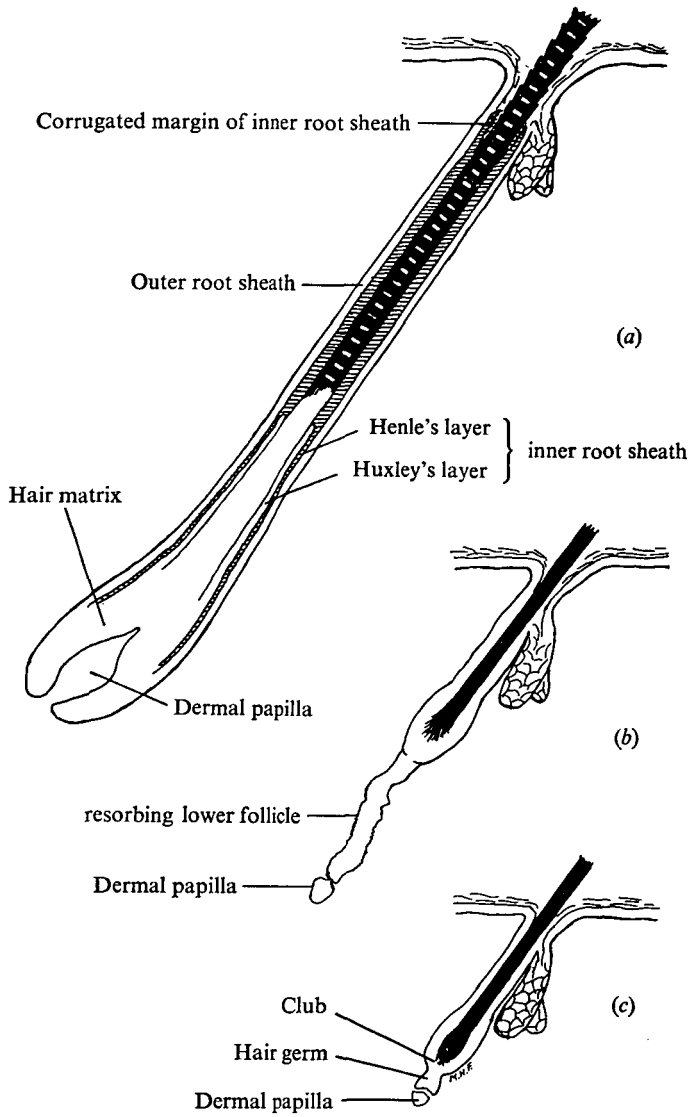
SUMMARY

Mice homozygous for the *asebia* mutation (*ab*/*ab*) are characterized by defective sebaceous glands, a short sparse hair coat from 7 days and progressive alopecia. In addition, we have found that the initial hair follicle rudiments in the skin of these mice are able to differentiate into relatively normal anagen follicles which are often excessive in length and have minor abnormalities of the inner and outer root sheath components. The inner root sheath fails to form the typical transverse corrugations at the level of the sebaceous glands and its cells apparently remain, partially undegraded, plugging the hair canal and adhering to emerging hair shafts. Defects noted in the outer root sheath may be responsible for the failure of inner root sheath degradation. With increasing age, irregularities in hair cycle duration, loss of the originally parallel arrangement of hair follicles and further abnormalities of the individual follicular components are increasingly evident. Follicles in asebic mice have a tendency to form buds and branches which occasionally begin typical follicular differentiation. The consistent failure of the asebic follicles to pass normally through the catagen stage to the telogen stage results in long twisted follicles with abnormal and often loosely anchored hair clubs. The dermal papillae are often abnormal or absent from telogen follicles, while typical germ cells are not formed. Thus the lack of multiple hair follicles, the disorganization of follicles and the progressive alopecia observed in the asebic mice are accounted for. It is suggested that the altered dermal environment and outer root sheath abnormalities may be responsible for many of the follicular defects.

1. INTRODUCTION

A hair follicle in the foetus of a mouse or other mammal develops by the downgrowth of a group of epithelial (basal epidermal) cells, together with the adjacent group of mesenchymal cells, into the dermis. The group of mesenchymal cells forms into a dermal papilla, and then the epithelial cells next to it divide rapidly while the daughter cells move towards the skin surface, differentiating into the

layers of the inner root sheath and the hair (Hardy, 1969). The initiation of the epithelial downgrowth results from a heterotypic interaction (Grobstein, 1965), in which the group of mesenchyme cells has been shown, by tissue recombination



Text-fig. 1. Scale drawing of stages of hair cycle in the normal mouse: (*a*) Anagen; (*b*) catagen; (*c*) telogen. ■, Keratinized zone of hair; ▤, hyalinized zone of inner root.

and transplantation studies (Kollar, 1970), to be the inducer of the epithelium. After a hair follicle has been established, the dermal papilla remains the inducer of new follicle growth (Oliver, 1967*b*, 1970) and appears to influence the size of the follicle and the rate of hair production (Cohen, 1965; Van Scott, 1965). However,

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the properties of the local dermis beyond the dermal papilla may also have a significant influence on follicle characteristics (Cohen, 1969), and indeed the long-term regional specificity of hair follicles and epidermis in adult mammals has been demonstrated to depend on influences from the dermis (Billingham & Silvers, 1967).

It is therefore not surprising that mice homozygous for *asebia* (*ab*/*ab*; Gates & Karasek, 1965; Gates, Arundell & Karasek, 1969), which show many abnormalities in both the dermis and the epidermis (Josefowicz & Hardy, 1978*a*) also show defects in hair follicle differentiation and in cyclic growth of hairs. In this paper it will be shown that the sparse coat which is characteristic of asebic mice is not merely a consequence of the sebaceous gland defect for which the name *asebia* was given. Rather it appears to be one of the consequences of a series of defects in the skin beginning before birth which impair the development of hair follicles. The nature of the sebaceous gland defect is described in a separate paper (Josefowicz & Hardy, 1978*b*).

2. MATERIALS AND METHODS

The observations were made on BALB/c mice carrying the *asebia* gene. Approximately 60 asebic (*ab*/*ab*) mice, ranging in age from newborn to two years, were compared with their phenotypically normal +/*ab* litter-mates. Pre-natal mice from 14 days to birth were also examined. Skin samples were taken from the mid-dorsal region of the trunk for the histological study of paraffin serial sections stained by a variety of techniques. Both the mouse colony and the microscopic techniques were described in detail previously (Josefowicz & Hardy, 1978*a*).

The hair follicles (Text-fig. 1) were studied in the anagen or growing phase and the telogen or resting phase of the hair cycle (Dry, 1926). The catagen phase is a short period of very rapid change that is not suitable for detailed comparisons between the two genotypes, which have hair cycles that are slightly out of phase. For a rough estimate of the average anagen follicle length in a dorsal skin sample, the length of the first three fully differentiated and maximally elongated longitudinally sectioned anagen follicles on one slide was measured to the nearest micrometre. Similar measurements were made on telogen follicles in samples of dorsal skin in the resting phase.

3. RESULTS

All +/*ab* mice developed a very dense coat of hair within the first three weeks after birth. Individuals of the same age showed little variation in density or average length of hairs. From 7 days after birth the *ab*/*ab* mice were distinguished by a sparser coat as well as a dry, scaly skin. Alopecia increased with each succeeding hair cycle, until very few scattered hairs remained on most of the body. A rough collar of stubby hairs persisted throughout life in the anterior thoracic region. Variation between individuals in the length and density of hairs was common in the *ab*/*ab* mice, but was less within litters and within families than between families.

Follicles of both asebic and normal litter-mates reached the telogen or resting

stage of the first hair cycle at 20 days after birth, but differences in hair cycle duration were obvious at the second cycle. While the follicles found in the skin of normal mice at 39 days had reached the telogen stage of the second cycle, those of the asebic litter-mates were still in the active anagen stage. Thereafter, the follicles of asebic and normal litter-mates became increasingly out of phase. The hair matrixes of the asebic follicles apparently remained mitotically active for longer periods of time. While the duration of telogen increased in succeeding cycles in the dorsal skin of normal mice, this trend was not apparent in the asebic dorsal skin.

(i) *Anagen follicles*

The growth of the first pelage hair follicles on the dorsum of asebic mice began normally about 14 days *post-coitum*. However, the process of differentiation was somewhat advanced when compared with that of their $+/ab$ counterparts during the remainder of foetal life. The follicular downgrowths were longer at 16 days *post-coitum* and by 18 days the inner root sheath (IRS) cones were more developed and extended farther up the longer follicles. Follicles from asebic mice 6 days and 11 days after birth were slightly longer than those of normal litter-mates during the period of follicle elongation. Measurements of nine fully elongated anagen follicles of the first and second hair cycles from three asebic mice provided a mean length of $2048 \pm 74{\cdot}7^*$ μm, which is significantly higher than the corresponding length of $946 \pm 50{\cdot}0^*$ μm from normal mice ($P < 0{\cdot}001$). Many follicles had an enlarged hair matrix (i.e. the mass of actively dividing epithelial cells of the hair bulb, Text-fig. 1*a*). This trend was also characteristic of asebic follicles in later hair cycles.

The inherent ability of the follicle rudiments in asebic mice to differentiate into all of the structures of anagen follicles (Text-fig. 1*a*) was apparently unaltered. However, in the more severe expressions of the mutation and in later hair cycles,

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PLATE 1

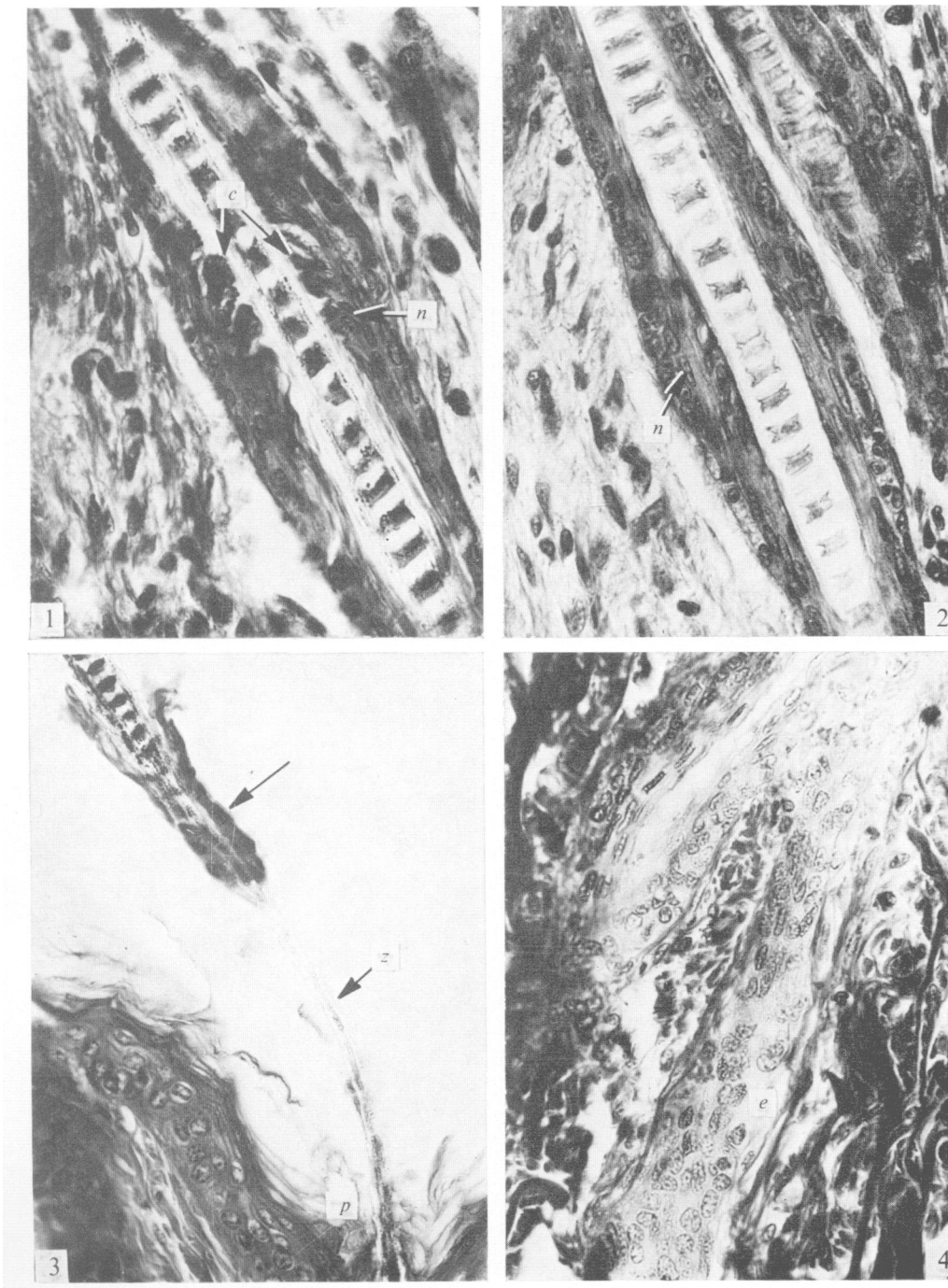
Fig. 1. The upper region of an anagen follicle from the mid-dorsal skin of a normal ($+/ab$) male, 8 days old. The transverse corrugations (*c*) of the IRS and the oval nuclei (*n*) of the adjacent ORS cells are seen. PAS-diastase treated, with Mayer's haemalum counterstain. × 550.

Fig. 2. The upper region of an anagen follicle from the mid-dorsal skin of an asebic (ab/ab) male litter-mate, 8 days old. Note that the IRS has no corrugations and that the adjacent nuclei (*n*) are elongated. PAS-diastase treated, with Mayer's haemalum counterstain. × 550.

Fig. 3. Emerging hair shaft from an (ab/ab) male, three months old. The zigzag hair fibre is sectioned longitudinally and shows a zone of constriction (*z*). Note the cellular material (arrow, which may have originated from the IRS) adhering to the hair shaft, and the plug (*p*) of keratinized material at the mouth of the hair canal. Mayer's haemalum, eosin and picric acid. × 425.

Fig. 4. Branching hair follicle found in the mid-dorsal skin of an ab/ab male, three months old. A fine hair shaft is visible. The extension (*e*) from the follicle is elongated but undifferentiated. Mallory's triple connective tissue stain. × 500.

* Standard error of the mean.



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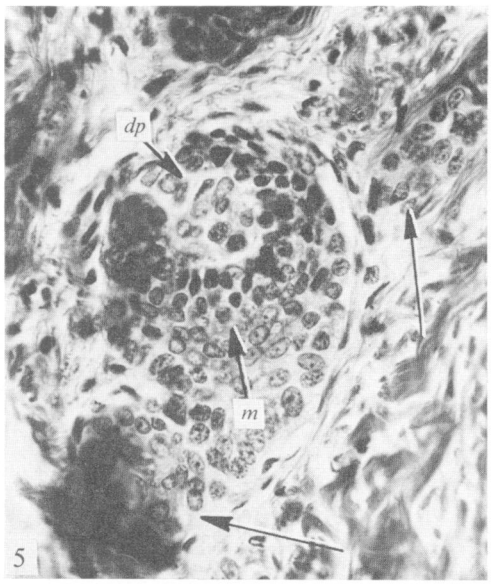

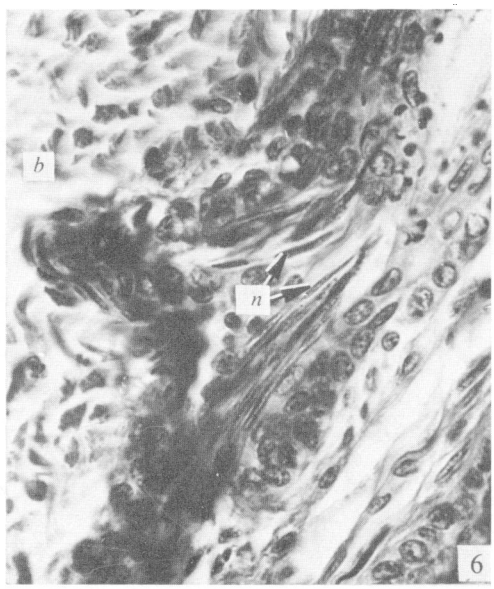

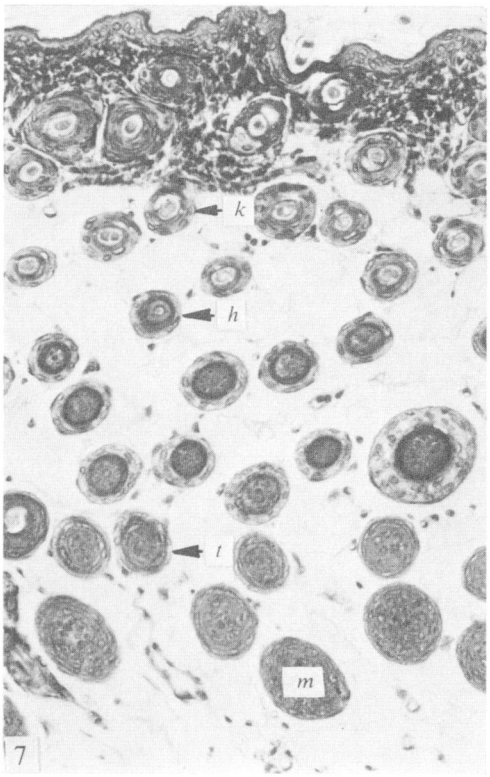

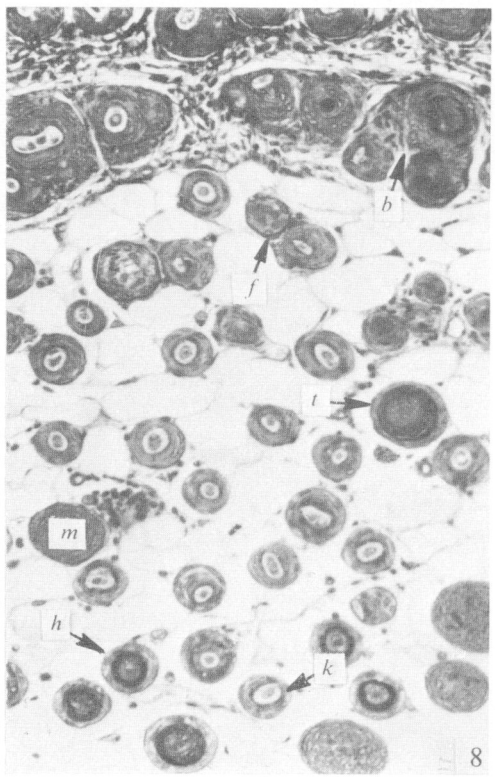

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there was a tendency for anagen follicles to become more twisted or structurally abnormal.

While the cells of the outer root sheath (ORS) of many asebic follicles were morphologically normal, those of the more twisted asebic follicles contained condensed, stellate nuclei. Variation in thickness of the ORS was more pronounced in asebic mice: in some follicles the ORS was three or four cells thick near the hair bulb but a flattened and barely distinguishable single layer of cells along most of the length of the follicle.

During anagen of the first hair cycle, the follicular inner root sheath (IRS), composed of Henle's layer, Huxley's layer and a cuticle, was significantly altered only at the uppermost level in the follicles of asebic mice. In normal mice, while the hair is emerging at the skin surface, the IRS cells hyalinize (i.e. lose their cytoplasmic staining and become hard and birefringent; Hardy, 1952), move up in the follicles, and, just below the level of the sebaceous glands, form a corrugated inner margin which partially interdigitates with cells having small oval nuclei and originating from the ORS (Text-fig. 1, Plate 1, fig. 1; Auber, 1950; Montagna & Parakkal, 1974). The staining characteristics of this corrugated zone of the IRS are very different from those of the IRS proper in normal mice. The folds were found to be PAS-positive and diastase resistant, as well as Alcian Blue-positive, particularly along the edge adjacent to the growing hair shaft. This PAS-positive band was rarely seen in the anagen follicles of asebic mice. When present it was short and narrow. The inner margin of the IRS was usually smooth in this region (Plate 1, fig. 2). Although in normal mice the adjacent cells of the ORS in this region were hypertrophied and contained rounded nuclei, the adjacent ORS cells in the asebic follicles were quite elongated, had flattened nuclei and did not interdigitate with IRS corrugations.

PLATE 2

Fig. 5. Budding hair follicle found in the mid-dorsal skin of an *ab/ab* male, three months old. An apparently normal hair matrix (*m*) enclosing a dermal papilla (*dp*) is budding from the ORS (arrows) of the original follicle. Mayer's haemalum, eosin and picric acid. × 550.

Fig. 6. Part of a budding hair follicle found in the mid-dorsal skin of an *ab/ab* male, three months old. The bud (*b*) has partially differentiated to form the early IRS components. The elongated nuclei (*n*) typical of the IRS are shown in the follicle and also in the bud. Mayer's haemalum, eosin and picric acid. × 550.

Fig. 7. Section vertical to the skin surface and at right angles to the direction of follicle slope, from a+/*ab* male, 15 days old. The hair follicles are in their typical parallel arrangement and the section shows the clearly demarked levels of follicle activity in the skin. m, Hair matrix; t, trichohyalin granule forming IRS cells; h, hyalinized IRS; k, keratinized hair shaft. Mallory's triple connective tissue stain. × 100.

Fig. 8. View in the same plane of section as Fig. 7, from an *ab/ab* male litter-mate, 15 days old, with the hair follicles in a similar parallel arrangement but showing an absence of any ordered levels of follicle activity. For example, a hair matrix (*m*) is seen at a higher level than many of the keratinized hair shafts (*k*). A branching hair follicle (*b*) and some undifferentiated follicular buds (*f*) are shown. t, Trichohyalin granule forming IRS cells; h, hyalinized IRS. Mallory's triple connective tissue stain. × 100.

Often during the second and subsequent hair cycles the IRS of asebic mice became abnormal in other respects. In the more severely affected follicles of asebic mice, at the level of the faulty sebaceous glands, the IRS cells had degenerated to an amorphous material containing condensed nuclei and nuclear fragments. The IRS material did not form transverse corrugations and disappear as it did in normal mice, but remained in this partially degraded form adhering to the shafts of many hairs (Plate 1, fig. 3) and contributing to the extensive accumulation of so-called 'keratinized' material forming plugs within the hair canals. The IRS showed fewer trichohyalin granules in Huxley's layer and a tendency to hyalinize deeper in the follicles – sometimes as far as the hair matrix.

While keratinization of the hair shaft was usually normal in the follicles of asebic mice, some incompletely keratinized fibres (identified by eosinophilia and failure to stain with picric acid) were seen emerging from the hair canal. Although all four fibre types (monotrichs, awls, auchenes, and zigzags; Dry, 1926) were formed by the asebic mice, the distinctive shapes of the different fibre types were more difficult to recognize in samples of their hair. Minor irregularities were also evident on the surface of hairs of asebic but not of normal mice, as previously reported by one of us (Geissinger, Josefowicz & Abandowitz, 1974). The average length of asebic hairs above the skin was considerably less than that of normal pelage hairs.

In some mature (fully elongated) anagen follicles of young asebic mice, masses of epithelial cells were seen budding from the ORS into the dermis below the level of the sebaceous glands or into the hypodermis. For the most part, these extensions remained undifferentiated (Plate 1, fig. 4). However, an obvious hair matrix with an enclosed dermal papilla, equivalent to stage 3 of follicle development (Plate 2, fig. 5), was seen budding from the ORS of one mature follicle. A bud from another follicle elongated deeply into the skin and partially differentiated to form an early IRS (equivalent to stage 4; Plate 2, fig. 6). A thickened Alcian Blue-positive band representing basement membrane material surrounded these downgrowths and was continuous with the basement membrane of the original follicle.

The originally parallel arrangement of follicles in the skin during the first hair cycle (Plate 2, figs. 7, 8), was lost in succeeding hair cycles in many asebic mice (Plate 3, fig. 9). Misshapen follicles followed a tortuous pathway towards

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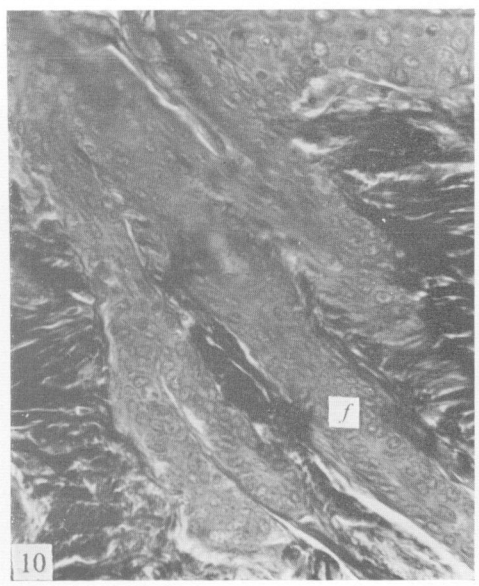
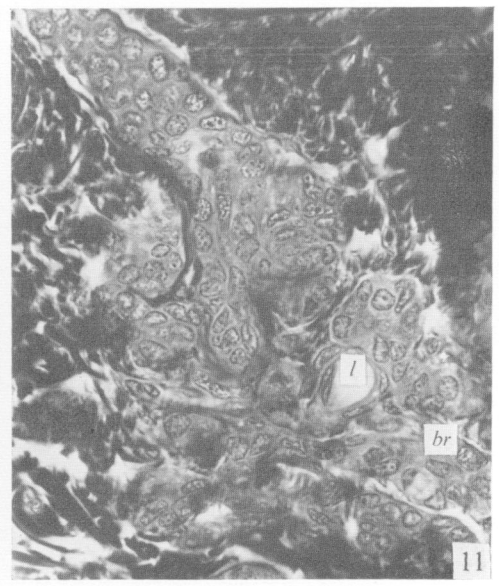
PLATE 3

Fig. 9. Section vertical to the skin surface from an *ab/ab* male, 4 months old. The parallel arrangement of hair follicles has been lost. Mallory's triple connective tissue stain. × 100.

Fig. 10. Mid-dorsal skin of an *ab/ab* male, 22 months old, showing a long branched epithelial downgrowth (arrows) which has remained histologically undifferentiated. Its origin appears to be independent of the adjacent hair follicle (*f*). Mallory's triple connective tissue stain. × 300.

Fig. 11. Metaplastic structure found in mid-dorsal skin of an asebic (*ab/ab*) male, 22 months old. The branches (*br*) and a lumen (*l*) of the gland-like structure are shown. Mallory's triple connective tissue stain. × 500.





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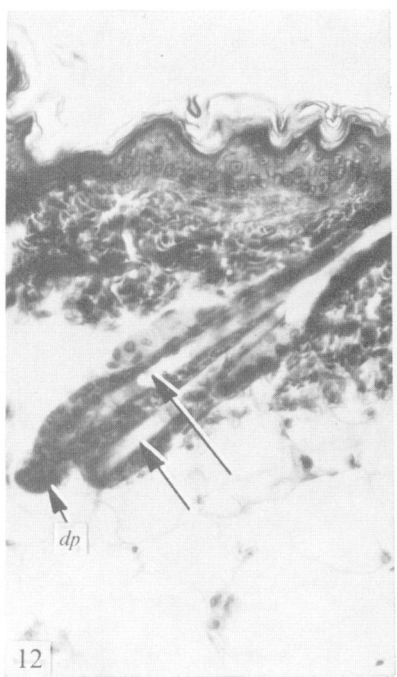

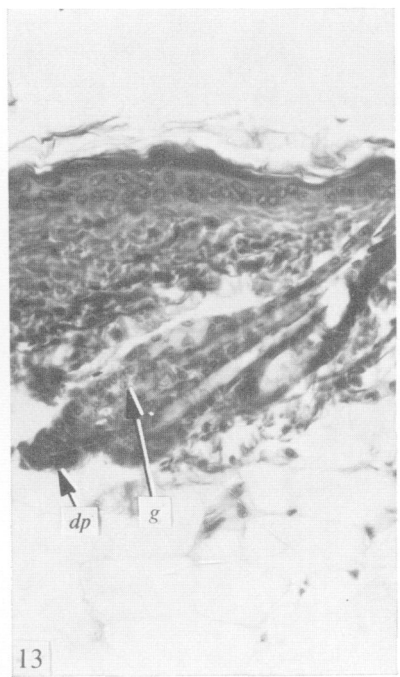

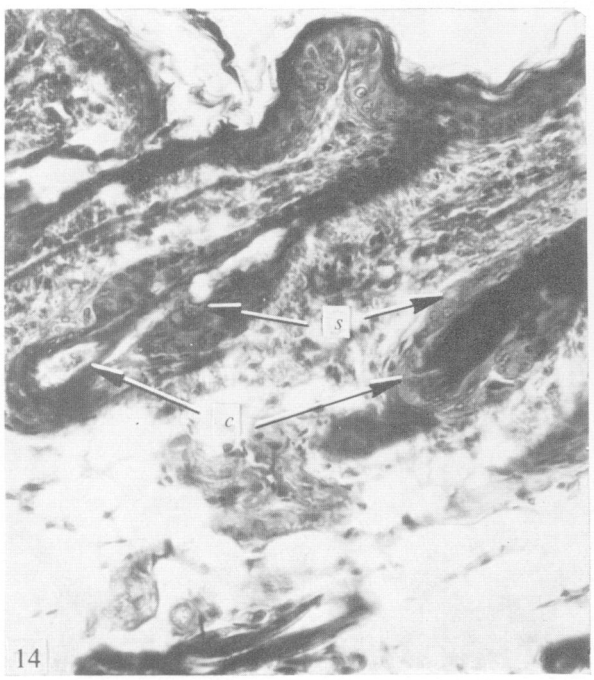

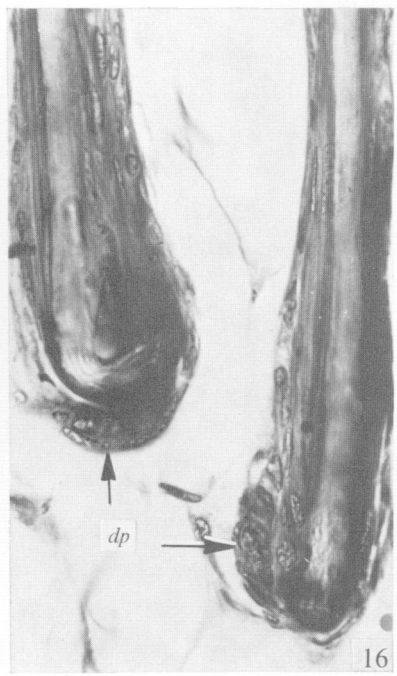

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the epidermis. Other follicles ran in random fashion, some parallel to the skin surface and some away from the surface.

In older asebic mice, characterized grossly by increased and sometimes almost total alopecia, either an obvious decline in the total number of follicles or a high proportion of abnormal or unproductive follicles was observed. Hyperplastic (budding or branching) follicles of the type described in the younger mutants were more common in the older asebic animals. Long epithelial downgrowths not associated with hair follicles were also seen in the older asebic skin (Plate 3, fig. 10). Although these structures were often branched, they remained histologically undifferentiated. Plate 3, fig. 11 shows one altered epidermal downgrowth which bore no resemblance to a hair follicle but had acquired a structure which suggested dichotomous branching. A small lumen was seen in several portions of this gland-like structure.

(ii) *Telogen follicles*

The most striking abnormality of the asebic skin was the failure of the hair follicles to progress normally from the active anagen stage through catagen to the normal telogen or resting stage (Text-fig. 1).

In normal (+/*ab*) mice part of the hair matrix and the lower part of the follicle were resorbed as the follicle shortened during the catagen stage. A fibrous club of modified cortex cells formed at the dermal level slightly below the sebaceous glands and was enclosed by modified outer root sheath cells with lobate nuclei constituting the hair 'germ' (Parakkal, 1970; Montagna & Parakkal, 1974). Directly below the club hair and the hair germ capsule lay a clump of cells representing the dormant dermal papilla. With the onset of anagen in the next hair cycle, the germ cells proliferated, enclosed the dermal papilla and grew down into the hypodermis to form another follicle base. The club hairs from the previous

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PLATE 4

Fig. 12. Multiple follicle found in the mid-dorsal skin of a +/*ab* male, 20 days old. Note the two hair shafts (arrows) and the dermal papilla (*dp*). Mallory's triple connective tissue stain. × 175.

Fig. 13. Another multiple follicle from the mid-dorsal skin of a +/*ab* male, 20 days old. Note the germ cells (*g*) with their lobate nuclei. *dp* – dermal papilla. Mallory's triple connective tissue stain. × 175.

Fig. 14. Two asebic telogen hair follicles found in the mid-dorsal skin of an *ab*/*ab* male, 20 days old. The hair clubs (*c*) are swollen and irregularly keratinized. s, Abnormal sebaceous glands. Mallory's triple connective tissue stain. × 175.

Fig. 15. The lower part of a telogen follicle extending deep into the hypodermis of the mid-dorsal skin of an *ab*/*ab* male, 20 days old. Note the irregularly shaped club (*c*), the absence of a dermal papilla, and the elongated nuclei of the attenuated ORS. Mallory's triple connective tissue stain. × 400.

Fig. 16. Two misshapen hair clubs lying parallel to the skin surface in the hypodermis, adjacent to the panniculus muscle, of the mid-dorsal skin of an *ab*/*ab* male, 20 days old. Note the abnormal position and morphology of the associated dermal papillae (*dp*). Mallory's triple connective tissue stain. × 400.

hair cycles were usually retained within the follicle (Plate 4, figs. 12, 13). This organized pattern of hair cycling leading to multiple hair follicles was not seen in the asebic skin.

Measurements of telogen follicle length showed a mean of $194 \pm 2{\cdot}7$* μm for 9 normal ($+/ab$) and $500 \pm 49{\cdot}3$ μm for 5 asebic (ab/ab) mice at various ages between 20 days and 2 years. On the average, the asebic telogen follicles were reduced to 25 % of the length of their anagen counterparts (see page 148), which is proportionately similar to follicle resorption during catagen in normal mice. However, because of the excessive length of the asebic anagen follicles, none rose in the skin to the level of the normal telogen follicles and most remained with their bases deep in the hypodermis. During resorption the asebic follicles became bent or twisted, and a malformed and distorted hair club formed at the base of the hair shaft. Many of the clubs were swollen and irregularly keratinized (Plate 4, fig. 14) and frequently appeared to be only loosely attached to the adjacent ORS cells. The ORS of most asebic resting follicles decreased in diameter to form a thin casing of flattened cells around the attenuated hair shaft and hair club (Plate 4, figs. 15, 16). None of the typical 'germ' cells (ORS cells with lobate nuclei) were observed. Relatively normal telogen follicles were rarely seen. An apparently normal resting dermal papilla did form in association with some of the distorted clubs, although it was often positioned alongside the follicle rather than beneath it (Plate 4, fig. 16). Dermal papillae were often separated from their respective follicles and sometimes no dermal papilla was found.

(iii) *Degenerating follicles*

The bases of hair follicles of asebic mice at all ages studied were prone to degeneration. This was particularly true of those follicles in the anagen stage of the hair cycle. Pycnotic nuclei were seen in the lower half of many hair follicles. Large numbers of polymorphonuclear leukocytes and eosinophils were associated with these degenerating structures.

4. DISCUSSION

This study confirmed and amplified the observations of Gates & Karasek (1965) on elongation of follicles, follicle plugging, absence of multiple follicles, and progressive alopecia in asebic mice of the same origin (BALB/cCrg1Ga). Nay (1972, 1973) also observed follicle elongation in asebic BALB/cJ mice, but the delayed telogen of the first hair cycle which he described did not occur in our colony.

Asebic mice had longer anagen follicles but shorter hairs than their normal litter-mates, and although the catagen stage of the first cycle began at about the same time as in normal mice, the length of subsequent anagen phases was significantly prolonged. These features, and the presence of excessively large

* Standard error of the mean.

hair bulbs suggest that the amount of mitotic activity of hair matrixes might not be as different from that in normal mice as observation of the sparse hair coat alone would indicate. Deeper growth into the hypodermis might be due to lessening of physical resistance in the altered dermis or to altered inductive influences from it.

Asebic skin possessed the ability for complete and relatively normal differentiation of hair follicle buds into the various components of the anagen follicles in the first hair cycle. The only abnormality consistently observed was the failure of the IRS to form transverse corrugations and disappear at the level of the sebaceous glands. Auber (1950), and Gemmell & Chapman (1971), working with sheep, and Straile (1965), working with several species, including mice, presented evidence for breakdown of IRS cells and extraction of some contents by enzymes originating from the adjacent modified ORS cells. The amount of IRS corrugation might be altered in asebic mice not only by changes in the levels or activities of lytic enzymes, but by changes in the balance between the upward movement of the IRS cells and the rate of degradation. The morphological abnormality of the ORS cells at this level in the asebic follicle, and the absence of the typical interdigitation of ORS and IRS cells, suggest that ORS cells may be responsible for the failure of IRS cells to degrade. The amorphous material plugging the pilary canal of asebic follicles and adhering to the emerging hair shafts contains undegraded IRS material. Sebaceous secretions may also be involved in normal IRS dissolution (Straile, 1965). Therefore, the abnormal secretions of asebic sebaceous glands (Josefowicz & Hardy, 1978*b*), as well as contributing to the debris retained in the pilary canal, could interfere with the degradation process of the IRS.

The capacity of ORS cells in asebic mice to form buds and branches which occasionally began follicle differentiation seems unusual but is not entirely without precedent. During the hair cycle in normal mice, certain ORS cells become hair germ cells and then hair matrix cells (Montagna & Parakkal, 1974). Some deep ORS cells of adult rat vibrissa follicles can be induced to undergo the same transformation when dermal papillae are transplanted (Oliver, 1967*a*, 1967*b*), and some developing mouse vibrissa follicles can be induced to form lateral buds and glands in vitro by excess vitamin A (Hardy, 1968). A similar transformation of ORS cells apparently occurs in asebic mice, but the dermal factors which may induce these changes are unknown.

The failure of the asebic follicles to pass normally through the catagen to the telogen phase is perhaps the most consistent abnormality noted in this study. Defects found in the structure of the ORS, and the previously reported defects in the connective tissue sheath (Josefowicz & Hardy, 1978*a*) may contribute to a lack of coordination in the complex events and movements of the catagen phase, leading to distension and twisting of the follicle base, as well as its failure to move up to a normal level in the skin.

In a normal mouse the hair germ and resting dermal papilla of a telogen follicle are situated in a modified dermis above a connective tissue track, left by the

receding follicle during catagen, which is thought to guide its movement during the next anagen phase (Roth, 1965; Moffat, 1968). The dermal papilla and the ORS germ cells of the asebic mouse, which have remained in the unnatural and possibly adverse environment of the hypodermis, might, if they survived, form an atypical or unhealthy anagen hair follicle that would also lack this guidance. Reduction in the number of emerging hairs and the loss of parallel orientation of follicles could, then, be a consequence of the altered environment of asebic follicles.

It appears that the hair club fails to form normally in many follicles of asebic mice and that the ORS cells are loosely associated with the hair club rather than tightly attached. Lacking the normal club cell formation which Parakkal (1970) considered to be crucial for anchoring the hair to the follicle, asebic mice are likely to shed prematurely those hairs which do emerge from the skin. This feature, when considered in conjuction with the inability of many disoriented hairs to emerge, and the abnormalities of the dermal papillae and germ cells, could account for the lack of multiple follicles and the progressive alopecia observed in the asebic mice.

Many of the follicle abnormalities have been linked to defects in the ORS cells. However, this is not necessarily the site of the primary defect. The increased prevalence of hair follicle abnormalities with successive cycles suggests that follicular changes may be a consequence of dermal or systemic changes. The very abnormal dermis (Josefowicz & Hardy, 1978*a*) may have affected the adjacent ORS cells, and may have been a mediator of the other changes observed in the follicles of asebic mice.

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