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'Bare', a new hairless mutant in the mouse—genetics and histology

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There are many reports in the literature on different types of hereditary hypotrichosis in mice. Gordon, in 1850, apparently was the first to report hairlessness in the house mouse. Since then, hairless specimens have been reported by several others in house mice, American deer mice and Asiatic tame mice. These conditions of genetic hairlessness fall into three main categories:

1. Mutants in which hair-loss took place by the shedding of entire hairs—viz. 'hairless' (David, 1931; Fraser, 1946; Montagna *et al.* 1952), 'rhino' (Howard, 1940), hairlessness in Asiatic tame mice (Makino, 1950), and 'hairless' in American deer mice (Rigdon & Packchanian, 1957).
2. Mutants in which hairlessness was produced by defective keratinization of hairs—e.g. 'Naked' (David, 1931; Fraser, 1946), Alopecia (Dickie, 1955), 'matted' (Searle & Spearman, 1957; Jarrett and Spearman, 1957).
3. Mutants which led to a complete absence or loss of certain types of hairs – e.g. 'crinkled' (Falconer *et al.*, 1951), 'Tabby' (Falconer, 1953); 'ragged' (Carter & Phillips, 1954).

Another new hereditary defect affecting the hair coat of Swiss albino mice and designated as 'bare' was first observed in February 1953 at the Poona Virus Research Centre. Later on at the I.C.R.C., similar hairless mice along with the normal ones were also born to Swiss parents. Since then, these mutant animals have been reared in the mouse colony at the I.C.R.C.. This new mutant, 'bare', belongs to the second category of hairless mutants, since the abnormality was observed in the keratinization of hair. The present report is on the genetics and comparative study of the hair growth in the normal and the mutant mice.

MATERIAL AND METHODS

In order to determine the precise mode of inheritance, five different breeding experiments between the normal and bare mice were conducted. Hair growth, hair pattern, hair types and other changes were observed daily in normal and bare mice from the time of their birth till they were 6 months old. The study of the hair follicles in the skins of the normal and bare mice was carried out in two ways:

(*i*) *Whole mounts of the epidermis*

Acetic acid digestion method was employed for preparing the whole mounts of the epidermis (Liang, 1948). The hairy and bare animals used were 1-day, 5-day

and 10-day-old. Five animals were used in each age-group. Small pieces of skins from the right side of the mid-dorsum were utilized. The epidermis was stained with Mayer's hematoxylin and mounted in Canada balsam with the basal epidermal layer uppermost.

(ii) Paraffin sections of the skins

The comparative histological study of the hair cycles of hairy and bare mice was based on skin specimens of both sexes of animals ranging from newborn to 6 months. A total of 200 mice were investigated. Small rectangular pieces of skin were removed from the right side of the mid-dorsum for this study. They were fixed in Bouin's fluid for 24 hours. Sections were stained with Ehrlich's hematoxylin and eosin. A few slides were also stained with Mallory's staining technique.

OBSERVATIONS

A. Genetics

As seen from the breeding experiments in Table 1, the appearance of only hairy offspring from the matings of hairy females with bare males suggested the recessive condition of the mutant. The segregation from the intercross matings gave

TABLE 1. *Segregation data for bare mice*

	Type of mating		Number of litters	Number of normal mice	Number of bare mice	Total
	Female	Male				
1.	+/+	*ba*/*ba*	5	40	—	40
2.	+/*ba*	+/*ba*	15	92	34	126
				(94·5)	(31·5)	
3.	+/*ba*	*ba*/*ba*	8	41	34	75
				(37·5)	(37·5)	
4.	+/+	+/*ba*	5	27	—	27
5.	*ba*/*ba*	*ba*/*ba*	4	0	30	30

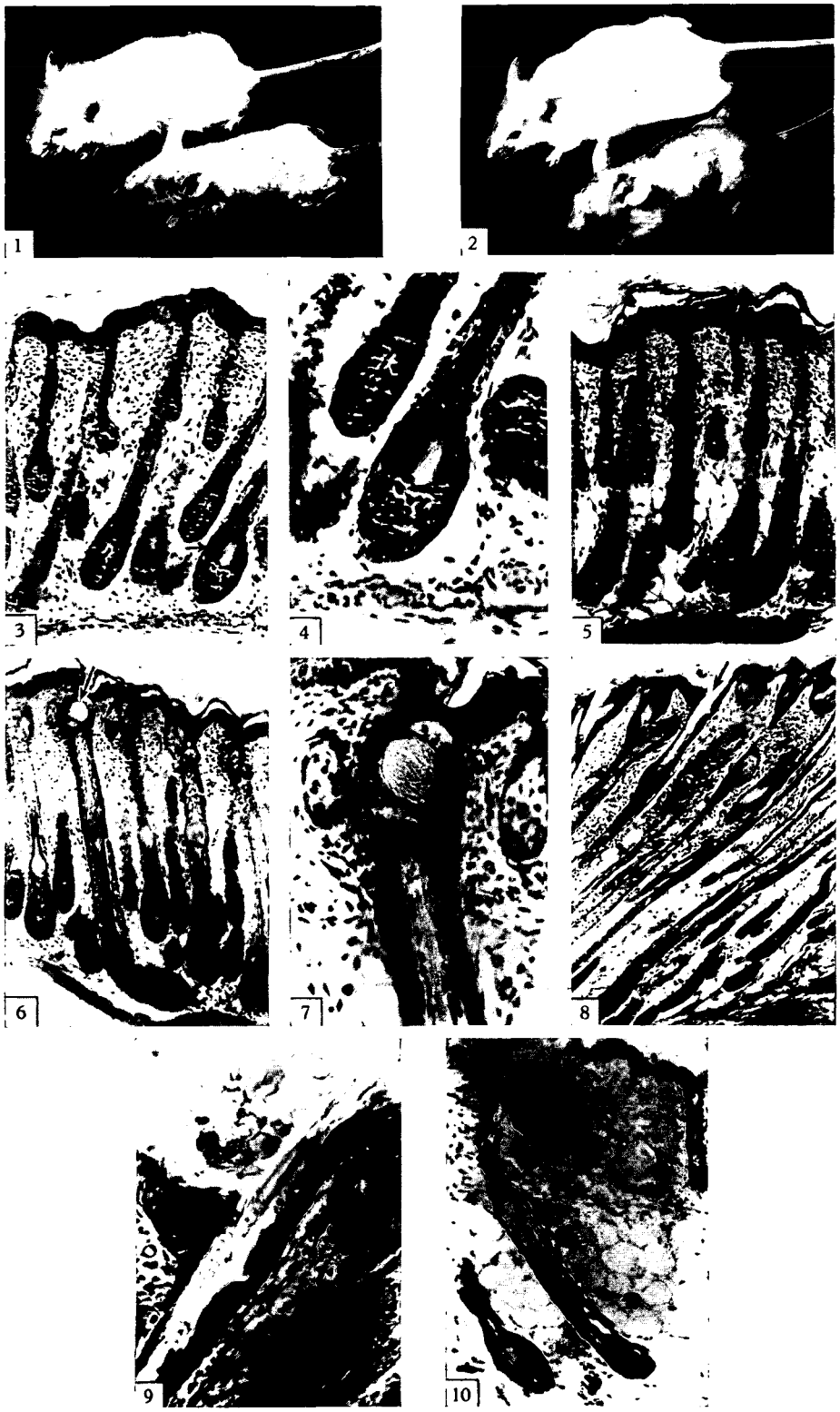
(The expected values are given in parenthesis.)

a ratio which did not differ significantly from the expected one of 3:1. Besides, the proportion of hairy to bare from the backcross mating was in a ratio of 1:1 as expected. In the fifth test, crosses between bare animals gave only bare offspring. These results further support the recessive nature of the mutant. These data indicate that the bare phenotype appears in animals that are homozygous for an autosomal recessive gene. The symbol *ba* has been suggested for this mutation.

B. Hair growth

1. *Gross examination*

The normal and the bare mice were of the same size at birth. They were all naked at birth except for the presence of vibrissae and other sensory hairs on the face in the normals. At 4 days small tiny hairs appeared on the head, neck and back of normal mice. By the tenth day the animals had a fine coat of hair. In bare mice, small fine hairs appeared at about 12 days after birth. They were first



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visible on the head, neck and shoulders and then covered the sides of the dorsum within 4 to 5 days. By the twenty-first or twenty-second day, the skin was covered with short, fine, sparse hairs till the thirtieth day (Fig. 1), after which the hairs were lost and the skin attained a smooth appearance. Some new hairs grew on the sides of the dorsum by about the age of 45 days which remained for 10 to 12 days more. Later, hair regeneration in monthly cycles, were noticed for 2 to 3 months more. At 6 months, the animals were strikingly naked except for some whiskers (Fig. 2). In very few mice, the head and back were always covered with small hairs which dropped off and redeveloped in cycles.

The eyes were normal except in a few cases where the animals were blind. The claws were also normal. The growth of bare animals was slower than the hairy ones and this difference increased steadily from the tenth to the thirtieth day. This difference in size persisted throughout life, though less marked in the older animals. These animals lived for about a year.

Samples of hair from the right side of the back of normal and bare mice were plucked from the root at 21 days for gross and microscopic examination. The four types of hairs, viz. guard hairs, awls, auchenes, and zigzags, were not distinguishable in bare mice. The hairs were small and thin as compared with the normals. The internal structure of the hairs of the mutant differed from that of the normals, since the number of rows of air cells was neither constant nor regular throughout the length of each hair as seen under the microscope.

2. *Microscopic examination*

The scanty and delayed hair growth suggested the absence of one or two types of hairs. Therefore, hair follicles in the whole mounts of the epidermis of hairy and bare mice were counted. In each skin sample, hair follicle counts were made at

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EXPLANATION OF PLATE

Fig. 1. Normal and bare mice (both 21 days old) showing the difference in the type of hair growth in them.

Fig. 2. Adult hairy and bare mice. The bare mouse is completely naked except for few hairs on the head.

Fig. 3. Globular keratinized mass in the bulb of one of the follicles, in the skin of a 4-day-old mouse (indicated by arrow). H. and E. $\times 100$.

Fig. 4. High-power picture of the same follicle indicated in Fig. 3. H. and E. $\times 200$.

Fig. 5. Normal hair development in the skin of a 4-day-old mouse. H. and E. $\times 100$.

Fig. 6. The skin of a 7-day-old mouse. The hair is at the epidermis. Globular swellings are present in the follicles. H. and E. $\times 60$.

Fig. 7. High power view of a hair follicle as seen in Fig. 6 (indicated by arrow) showing keratinized mass at the epidermis. H. and E. $\times 200$.

Fig. 8. The skin from a 14-day-old mouse. The hair is outside of the skin. H. and E. $\times 60$.

Fig. 9. High-power view of the follicle (indicated by arrow) in Fig. 8. H. and E. $\times 200$.

Fig. 10. Skin of 6-month-old bare mouse. The follicles with abnormal hair are below the resting ones. H. and E. $\times 100$.

a magnification of 10 × 10, in twenty-five fields each of 2 mm. square area. Table 2 gives the results of the mean values of the total number of follicles of the five skin specimens. The 'students' *t*-test was applied to find out whether there was any significant difference in the mean number of follicles in any age group. The values

TABLE 2. *Hair follicle counts in normal and bare mice*

Age	Mean values of the total number of follicles of five skin samples		Values of *t*	*P*
	Normal	Bare		
1 day	31	27	0·803	$0{\cdot}5 > P > 0{\cdot}4$
5 days	35	38	0·654	$0{\cdot}6 > P > 0{\cdot}5$
10 days	25	26	0·218	$0{\cdot}9 > P > 0\,8$

of *t* at different age-groups in hairy and bare animals are also given in the table. There was no significant difference in the mean number of follicles in the skins of hairy and bare animals as found by the *t*-test.

Dry, in 1926, divided the hair cycle of mice into three stages according to the growth of the hair follicles:

Anagen—growing phase of the follicle.

Catagen—transitional phase.

Telogen—resting phase.

The growing phase was further subdivided by Chase (1954) into six substages on the basis of the morphological changes in the development of the hair follicles. In this study, the terminology of Chase has been used throughout in referring to the various developmental stages.

In the first three stages of anagen, no difference was perceptible between the normal and bare mice. During this period, the development of the hair follicles was confined to the formation of the three layers in the cone of the internal root sheath. Sebaceous glands were present at the mouth of the follicles.

Anagen IV. The first visible abnormality in the skins of bare mice was observed in anagen IV. In the skins of 4-day-old bare mice, some distinct changes were found regarding the development of hair (Figs. 3 and 4). The normal pattern of the cells of the three concentric layers of hair (Fig. 5), viz. cuticle, cortex and medulla, which arose from the bulb and moved upwards was entirely missing. Instead, a mass of cells with deeply stained nuclei were seen in the central part of the bulb of some follicles. In others, globular masses were found in the bulb just above the dermal papilla. The globular masses consisted of a central shiny yellow portion surrounded by layers of deeply staining cells. All the follicles showed an abnormal type of hair development.

Anagen V. In 6-day-old hairy animals, the hair was found at the epidermis. In 7- to 8-day-old bare animals, the development of the hair was still poor as it reached the level of the epidermis. The hair still presented globular swellings in some part of the follicle (Figs. 6 and 7) . The bulged hair obliterated all the layers

leaving an external root sheath. Even in the straight hair wherever present, there was neither firmness nor rigidity, which was the characteristic feature of the normal keratinized hair.

Anagen VI. In 7- to 8-day-old normal mice, the straight keratinized hair was outside the epidermis. In 13- to 14-day-old bare mice, the hair emerged through the epidermis. All the follicles were long and slender with poorly keratinized hair in them. The lumps were no longer visible in any of the follicles (Figs. 8 and 9).

Catagen and telogen stages appeared normal. Sebaceous glands were larger as compared to those in the normal in the resting phase.

Along with different stages in hair growth, there were corresponding changes in the whole skin. The epidermis thickened with hair growth and remained the same, which was not so in the skins of the normal animals. The dermis and hypodermis increased in thickness with hair growth.

No further changes were observed in the skins of bare animals. The same abnormal hair picture was repeated in successive hair cycles, so that in 6-month-old skins some follicles with abnormal hair were below the resting ones (Fig. 10).

DISCUSSION

The bare mutant is of interest, since it is phenotypically distinct from the mutants described previously and represents a new type of hereditary hair loss in the mouse. Microscopic study of their skins also revealed a defect, not described previously in the development of hair, and so the mutant is of added importance in giving new information about normal hair growth.

Abnormal growth of hair in mice has been investigated morphologically, histologically and histochemically by a number of workers, among whom a particular mention may be made of Fraser (1946), Montagna *et al.* (1952), Searle & Spearman (1957) and Jarrett & Spearman (1957). All the hairless strains studied so far had vibrissae at birth, except for homozygous Naked mice which could be recognized at birth by the lack of vibrissae. In the present bare mice also, the absence of vibrissae and other sensory hairs at birth allowed them to be easily differentiated from the normal ones. In other mutant animals, the first signs of hair appeared between 4 to 8 days after birth, and the depilation in some began after 12 to 14 days. In the bare mice, however, the first signs of hair were visible at 11 to 12 days. These tiny hairs remained on the body of the animals for 12 to 15 days more and then disappeared at about the thirtieth day. This pattern of hair growth and hair loss distinguished the bare animals from the other hairless strains. The skin in older animals remained smooth instead of being thickened or folded as found in rhino and hairless mice.

The fact that the emergence of hair was delayed by about 8 days suggested that the primary defect might be in the formation of hair follicles. Whole mounts of the epidermis of 1-day-, 5-day- and 10-day-old animals showed no diminution in the number of follicles as compared with those of the control. The scanty growth of hair was due to some defect in the development of hair as seen from the micro-

scopic examination of the skins. The histology of the skins revealed keratinized globular masses in the follicles, suggesting some defect in the formation of the straight medullated hair. The same abnormal hair picture was repeated in all the hair cycles. It is thus clear that the bare mice are different from all the other mutants reported so far.

The cause of this abnormality is still not clear. In normal mice, the keratinization of hair is a gradual process that takes place along the entire length of the hair root and is completed in the middle part of the hair. The skins of bare mice also show the presence of different stages in the development of hair. These changes in the beginning are not visible at different levels in the follicles. Instead, in 4-day-old mice, yellow keratinized masses appeared in the bulbs of the follicles. This suggested that the entire keratinization of hair took place in the bulb of the follicle. The progress of hair development in the anagen stages IV, V and VI was therefore delayed. Later on, at 6 to 7 days, owing to cellular multiplication in the matrix, the keratinized hair made its way up the follicle. Then, the cells of the cuticle, cortex and medulla which formed the hair could be clearly seen in the bulb of the follicle. The first signs of hair outside the skin were at about 13 to 14 days of age of the animals. Even then, the erupted hair was of poor quality, small and thin as compared with the normal.

The histological study revealed some disturbance in the early stage in the development of hair, giving rise to poor hair growth.

SUMMARY

1. A new hereditary defect affecting the hair coat of Swiss albino mice is described. The defect was found to be inherited as a recessive character and is designated as bare (*ba*).

2. The gene affected the vibrissae as well as pelage hairs. The lack of vibrissae and other sensory hairs at birth, helped to differentiate them easily from the normal animals. The first hairs on the body appeared at 13–14 days of age. The hairs were thin and tiny and remained there till about the thirtieth day. The hairs in the second hair cycle appeared at about 45 days, and again disappeared within 10 days. The animals were entirely naked when they were 6 months old.

3. Gross as well as microscopic examination of hairs in the first hair cycle did not show the four different normal types of hairs. The hairs were comparatively very small, thin, and the internal structure did not show any regularity in the arrangement of the air cells.

4. No difference was found in the number of hair follicles in the bare and the normal Swiss mice.

5. Histology revealed the presence of keratinized globular masses instead of straight hair. This abnormality persisted in all the hair cycles.

6. The bare mice were compared with the other mutants and placed in the Alopecia-Naked group where the abnormality was in the keratinization of the hair.

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