The tabby locus (*Ta*) in the mouse: its site of action in tail and body skin

By PAMELA R. PENNYCUIK and KATHRYN A. RAPHAEL

CSIRO, Division of Animal Production, P.O. Box 239, Blacktown, N.S.W., 2148, Australia

SUMMARY

By means of grafting skin in which the epidermis of one genotype was combined with dermis of another to a nude host, we have shown that the effect of the mutant at the tabby (*Ta*) locus on follicle initiation in tail skin was not confined to either the epidermis or the dermis, that the effect of *Ta* on the morphology of body hairs was determined by the epidermis but that the close proximity of epidermis of a different genotype also affected body hair morphology.

1. INTRODUCTION

In the mouse, the sex-linked gene tabby (*Ta*) affects the initiation of hair follicles and the morphology of the coat hairs. In homozygous females (*Ta/Ta*) and hemizygous males (*Ta/*Y) *Ta* causes a reduction in the number of follicles destined to produce coat hairs and almost eliminates the initiation of follicles on the tail (Falconer, 1953; Claxton, 1967). It also causes all coat hair follicles to produce hairs of one type, namely straight hairs without constrictions but with some irregularities of the medullary cells (Grünberg, 1969). These hairs, which are usually regarded as modified awls, are morphologically quite distinct from the guard hairs, awls, auchenes and zigzags found in the coats of wild-type mice (Dry, 1926). In heterozygous females (*Ta/+*) initiation of hair follicles on the body and tail is unaffected by *Ta* (Kindred, 1967; McLaren, Gauld & Bowman, 1973) but hair morphology is modified. The coats of black agouti animals appear striped; both wild-type and tabby-type hairs are present in both the dark and light bands but zigzags form a higher proportion of the hairs present in the light than in the dark bands (Kindred, 1967).

The morphological effects of the tabby mutant in all genotypes could be due to its activity in the dermis, the epidermis or in both skin layers. Sofaer (1974) studied follicle initiation in skin grafts in which *tail* epidermis from wild-type or tabby embryos was combined with tail dermis from tabby or wild-type embryos (skin recombinants). He found that fewer of the recombinants incorporating tabby dermis produced follicles than recombinants incorporating tabby epidermis and he concluded that, although his results were insufficient to implicate the tabby dermis, they did not provide evidence of primary epidermis involvement. Mayer

& Green (1978) on the other hand studied the morphology of coat hairs in recombinants of *body* epidermis and dermis from wild-type and tabby embryos and found that only explants incorporating tabby epidermis produced tabby-type coat-hairs. They concluded, therefore, that the tabby gene acts in the epidermis. Sofaer (1974) used the chorioallantois of the chick as a host for his grafts whereas Mayer & Green (1978) used the testis of histocompatible males. The difference in the conclusions reached in these two studies could be due to differences in the site of action of the gene with respect to the initiation and the morphogenesis of follicles and hairs or to differences in the experimental techniques.

This paper describes the results of experiments designed to determine the site of action (dermal or epidermal) of *Ta* with respect to follicle initiation on the tail and with respect to body hair morphology by grafting recombinants from both skin regions to the nude mouse. It also presents results of an experiment designed to determine whether epidermis of one genotype has any effect on the morphology of hair growing on epidermis of a second genotype when both are closely juxtaposed.

2. METHODS

(i) *Mouse stocks*

Two random-bred wild-type stocks, a coloured and an albino, were used to produce wild-type embryos and mice of 3–4 weeks of age from which we obtained samples of tail skin and samples of mid-side body hair.

A random-bred coloured stock carrying *Ta* (originally imported from the Institute of Animal Genetics, Edinburgh) was used to produce *Ta/Ta* and *Ta/Y* embryos and 3 to 4 week old mice for tail skin samples.

A random-bred albino stock carrying nude (*nu*) produced the *nu/nu* mice used as hosts for skin grafts.

All stocks were maintained under conventional conditions.

(ii) *Preparation of embryonic skin pieces*

In +/+ embryos the first body hair follicles begin to appear at about 14 days post-conception (Claxton, 1966) and tail hair follicles at about 16 days (Falconer, Fraser and King, 1951); in tabby embryos the appearance of the first body hair follicles is delayed until about 17 days (Claxton, 1967) and few, if any, tail hair follicles develop. Embryos of 13, 14 and 15 days were therefore used as a source of skin pieces for preparing recombinants of epidermis and dermis of like developmental age as well as recombinants of like chronological age. These embryos were produced by timed matings; the morning on which the vaginal plug was found was considered day 0 of pregnancy. Following dissection from the uterus, the embryos were placed in Tyrode's solution at 4 °C.

Tail and body skin pieces for grafting were obtained from each embryo. Tail pieces were prepared by removing the distal and proximal quarter of the tail, cutting the remaining section in half longitudinally and removing the central core from the cut halves. Pieces of body skin were prepared by cutting 3 × 2 mm pieces

from both flanks and removing the adherent muscle. Some skin pieces of both types underwent no further treatment before grafting (explants); others were separated into dermis and epidermis and recombined in various ways before being transferred to the nude host (recombinants). Following removal from the embryo the explants were exposed to Tyrode's solution at 4 °C for 2–4 h before being transferred to petri dishes containing agar-based culture medium. The skin pieces to be separated into epidermis and dermis were exposed to 1 % trypsin (Difco 1:250) in Tyrode's solution at 4 °C for a period sufficient to effect separation: 1·5–2 h for tail skin pieces and 13-day body skin pieces and 3·5–4 h for 14-day body skin. Following separation, the dermal and epidermal pieces were recombined in petri dishes containing agar-based culture medium (Raphael & Pennycuik, 1980). Both explants and recombinants were incubated overnight in a tissue culture incubator (37·5 °C; 5 % CO_2).

(iii) *Grafting and observation of grafts*

Following 24 h incubation the explants were grafted to healthy, 5-week old nude mice (Raphael & Pennycuik, 1980). The grafts were examined at 2–5 day intervals for signs of pigmentation, thickening and hair eruption. When the grafts were 36 days old (post-conception) they were photographed, removed from the host and fixed in formol saline.

All grafts were omitted from the experimental results if the host died before the graft reached 36 days of age. In addition tail skin grafts were omitted if they showed no signs of pigmentation or thickening. Body skin grafts incorporating only one type of epidermis were omitted if no hairs erupted and grafts with adjacent pieces of tabby and wild-type epidermis were omitted if the tabby and wild-type areas in the grown graft were of very different sizes.

Successful tail skin grafts ranged in appearance from those with no hair to those with complete hair cover. For the purposes of comparing the experimental groups, each graft was allocated to one of five classes, as follows. (i) Lacking hair entirely (Plate I, fig. 4), (ii) with irregularly arranged hair (Plate I, fig. 5), (iii) with a fringe of hair around the graft border (Plate I, fig. 6), (iv) with a dense fringe of hair at the border and with a less dense cover on the centre (Plate I, fig. 7), and (v) with dense hair cover over the entire surface (Plate I, figs. 3, 8).

Successful grafts of body skin incorporating only one type of epidermis were classified as those with, and those without, zigzags using samples of 50–100 hairs plucked from the centres of the grafts. When present, the proportion of zigzags was determined. In successful grafts of body skin incorporating tabby epidermis adjacent to wild-type epidermis, hair samples were plucked from the centre of the pigmented (tabby) area, the centre of the albino (wild-type) area, and from the junction between the two. Hairs from the junction sample were then classified into two groups on the basis of pigmentation. We then determined the proportions of zigzags (including occasional septate hairs with one constriction), wild-type awls (straight hairs with four or more regularly arranged medullary cells per row) and tabby-type hairs (straight hairs with three or fewer irregularly arranged medullary cells per row) in the pigmented and albino samples, and the same classification was performed for the pigmented and albino hairs from the junction sample.

3. RESULTS

(a) Hair follicle initiation – tail skin

(i) Tail skin explants

When Sofaer (1974) grafted explants of tabby tail skin to the chick chorioallantois the successful grafts produced hair follicles. We grafted tail skin explants from wild-type (+) and tabby (Ta) mice to nude hosts to see if this host, too, caused changes in the appearance of the skin. The explants were taken from both 14- and 15-day embryos to see if the age of the donor had any effect on the appearance of the grafts.

Table 1. *Numbers of wild-type* (+) *and tabby* (Ta) *tail skin explants which produced successful grafts and numbers in each of the five morphological categories*

Genotype	Age of donor embryo (days)	No. successful grafts	Distribution of hair on graft				
			None	Irregular	Edge only	Edge and centre	Even cover
+	14	12	4	0	1	0	7
	15	6	0	1	0	0	5
Ta	14	11	5	4	2	0	0
	15	8	1	2	2	0	3

At 36 days post-conception the appearance of all + grafts was very different from that of +/+ tail skin left *in situ* (compare Plate I, figs. 1 and 3). Because expansion of the grafted skin was restricted by the size of the graft-bed on the nude host, the grafted skin became folded. This folding caused the scales to become tilted through an angle of 90°, a movement which brought each thickened scale border with its triplet of hairs into close proximity with its neighbour. The percentage of 14-day explants which produced grafts with an even hair cover was smaller than the percentage of 15-day explants which produced grafts of this type (Table 1). This reduction in the percentage of 14-day explants with hair may have been due to the fragility of the skin pieces.

At 36 days post-conception the appearance of *Ta* grafts, too, was very different from that of *Ta* tail skin left *in situ* (compare Plate I, figs. 2 and 4–8). In all grafts the skin surface was folded like that of + grafts but, in addition, many of the grafts produced hairs similar to those on + grafts. In two of the 14-day grafts and two of the 15-day grafts these hairs formed a fringe around the graft border. In three of the 15-day grafts the hairs formed an even cover across the graft surface and the appearance of the grafts was indistinguishable from that of successful + grafts. No grafts of this latter type were observed among the 14-day explants (Table 1). This failure of 14-day explants to produce any grafts with an even cover of hair could have been because the explants were removed from the embryo two days before follicles were initiated. They would therefore have had a longer period than 15-day explants to recover from the experimental manipulations before the follicles began to form.

The presence of a fringe of hair around the border of some of the tabby grafts could have been due either to diffusion of an inhibitor from the explant before or after it was transferred to the nude host or to diffusion of a follicle initiator from the host skin to the explant (Sofaer, 1974). In the first experiment with tabby

Table 2. *Numbers of wild-type* (+) – *tabby* (Ta) *recombinants incorporating tail dermis* (T) *and either tail* (T) *or body* (B) *epidermis which produced successful grafts and numbers in each of the five morphological categories*

Genotype and regional source epidermis/dermis	Ages of donor embryos (days)	No. successful grafts	Distribution of hair on graft				
			None	Irregular	Edge only	Edge and centre	Even cover
Tail/Tail							
+T/+T	15/15	13	3	5	0	0	5
+T/*Ta*T	15/15	8	0	0	0	0	8
*Ta*T/+T	15/15	11	1	4	0	0	6
*Ta*T/*Ta*T	15/15	15	1	7	2	2	3
Body/Tail							
+B/+T	14/14	8	1	1	0	0	6
+B/*Ta*T	14/14	5	0	0	0	0	5
*Ta*B/+T	14/14	17	10	1	0	0	6
	15/15	5	1	0	0	0	4
*Ta*B/*Ta*T	14/14	15	11	2	1	0	1
	15/15	3	0	0	1	2	0

explants the time in Tyrode's was not strictly controlled. In order to test whether diffusion of an inhibitor from the explant during exposure to Tyrode's was responsible for the variability in the appearance of the grafts, explants of 15-day skin were either transferred directly to the agar plate or were exposed to Tyrode's for 2 or 4 h before transfer. There were no significant differences among the groups.

We concluded that, apart from the tilting of the scales, the explants of wild-type tail skin behaved like tail skin *in situ* but that tabby tail skin explants grafted to a nude mouse, like tabby tail skin grown on the chick chorioallantois, grew more hair than skin from the middle section of the tails of *Ta* mice. Furthermore tabby grafts tended to grow more hair at the graft border than at the graft centre but this distribution of hair was not due to loss of an inhibitor during preparation of the graft.

(ii) *Recombinants of tail epidermis and tail dermis*

In Sofaer's experiment recombinants incorporating both *Ta* epidermis and *Ta* dermis produced fewer follicles than recombinants incorporating + epidermis and + dermis and recombinants incorporating *Ta* in only one of the skin layers. Table 2 summarizes the results of grafting the same four recombinant types to nude mice. Recombinants incorporating wild-type tail epidermis and wild-type tail dermis (+T/+T) behaved like + explants although the proportion of grafts with an even hair cover was reduced in the recombinant group (compare Tables 1 and 2).

Both recombinants of wild-type epidermis with tabby dermis (+T/*Ta*T) and

recombinants of tabby epidermis with wild-type dermis ($TaT/+T$) produced a proportion of grafts with an even crop of tail hair but they produced no grafts with a fringe of hair at the graft edge. Tabby epidermis, therefore, was able to respond to signals from wild-type dermis in at least some recombinants and tabby dermis was able to induce follicle development in wild-type epidermis.

Recombinants of tabby epidermis and tabby dermis (TaT/TaT) also produced grafts with tail hair. Some produced an irregular crop of hair and some an even crop of hair across the graft surface, but, in addition, in four of the grafts, the hair formed a fringe around the border of the graft like grafts of tabby explants. That is, the fringed grafts were characteristic of unseparated tabby tail skin and of recombinants with the tabby mutant in both the epidermis and the dermis.

Our results, using the nude mouse as host, therefore, confirm Sofaer's finding using the chick chorioallantois, namely that the effects of the mutant on follicle initiation are most marked when Ta is present in both epidermis and dermis.

(iii) *Recombinants of body epidermis and tail dermis*

In recombinants of epidermis and dermis from different body regions the dermis is able to induce the development of epidermal structures characteristic of the body region from which it was derived but the epidermis still retains some of the characteristics of its regional origin (Kollar, 1970; 1972). The ability of both $+$ and Ta tail dermis to induce the development of tail hairs in body epidermis and the ability of the body epidermis to retain its regional character were tested by preparing all four possible recombinants, i.e. wild-type body epidermis – wild-type tail dermis ($+B/+T$), wild-type body epidermis – tabby tail dermis ($+B/TaT$), tabby body epidermis – wild-type tail dermis ($TaB/+T$) and tabby body epidermis – tabby tail dermis (TaB/TaT). Because follicles appear earlier on $+$ epidermis (14–15 days) than on Ta epidermis (17 days) we used 14-day wild-type epidermis in the recombinants incorporating that epidermis and both 14- and 15-day tabby epidermis in the recombinants incorporating it. Both 14- and 15-day dermis were used in the tabby recombinants.

In all four recombinant types a proportion of the grafts grew hair and this hair was always of the tail type, i.e. the origin of the dermis determined the type of hair produced by the graft. The appearance of all successful recombinants incorporating body epidermis was similar to that of the corresponding recombinants incorporating tail epidermis. Recombinants $+B/+T$, $+B/TaT$ and $TaB/+T$ produced a proportion of grafts with an even hair cover but no grafts with a fringe of hair; recombinants TaB/TaT produced two grafts with a fringe of hair and two grafts with a fringe of hair and a sparse covering of hair on the graft centre. There was no evidence that the ages of the donor embryos affected the appearance of TaB/TaT grafts (Table 2).

Thus only recombinants incorporating Ta in both epidermis and dermis produced grafts with a fringe of hair around the border.

The results of these experiments with tail skin explants and recombinants indicate that tabby tail skin often grows hair when transplanted to a foreign host and that the effects of Ta on follicle initiation are most marked when the mutant is present in both skin layers. The observation that many of the grafts of Ta skin are bare in the centre but bordered with a fringe of hair support Sofaer's (1974)

explanation for the presence of follicles on tail skin grafts, namely, that a diffusible substance is involved in producing the tabby phenotype.

(b) *Morphology of pelage hairs–body skin*

(i) *Body skin explants*

The tilting of the scales on explants of tail skin grafted to nude hosts indicated that lateral growth of embryonic skin was restricted by the size of the graft bed. In order to examine whether this restriction had any effect on hair growth on body skin, explants of + and *Ta* skin were grafted to nude hosts. Hair samples from these grafts were compared with samples from wild-type and tabby mice of the same developmental age. The samples from the + grafts included as many zigzags as samples from wild-type mice and the samples from the *Ta* grafts included only tabby-type hairs. It was concluded that grafting had no effect on the morphology of body hair.

(ii) *Recombinants of body epidermis and body dermis*

Of the hair samples plucked from the recombinants examined by Mayer & Green (1978) only those from recombinants incorporating wild-type epidermis contained zigzags. Those incorporating tabby epidermis produced only tabby-type hairs. We examined hair samples from body skin recombinants of the same four types examined by Mayer & Green, namely wild-type epidermis – wild-type dermis (+ B/+ B), wild-type epidermis – tabby dermis (+ B/*Ta*B), tabby epidermis – wild-type dermis (*Ta*B/+ B) and tabby epidermis – tabby dermis (*Ta*B/*Ta*B). Because differences in the timing of follicle initiation in + and *Ta* embryos could have affected the results, we prepared recombinants of epidermis and dermis of different ages as well as recombinants of the same age.

Hair samples from all + B/+ B recombinants contained zigzags (Table 3) and the mean percentage of zigzags in these samples was similar to that in samples from + explants (Table 4). Irrespective of the age of the epidermis or dermis used to prepare the recombinants, hair samples from + B/*Ta*B recombinants also contained zigzag hairs. The percentages of zigzags in these samples was not very different from those in samples from + B/+ B recombinants, in spite of the difference between the primary : secondary follicle ratio in wild-type and tabby mice (Claxton, 1967). This suggests that tabby body dermis may be able to initiate as many follicles in + epidermis as wild-type dermis.

Hair samples from *Ta*B/+ B and *Ta*B/*Ta*B recombinants contained only straight hairs like those from tabby mice. The ages of the epidermis and dermis used to prepare the recombinant had no effect on the result (Table 3).

Our results, therefore, show that the morphology of the coat hair produced by recombinants grown on nude hosts, like the hairs produced by recombinants grown under the testis capsule (Mayer & Green, 1978), was determined by the genotype of the epidermis.

(iii) *Recombinants of tail epidermis and body dermis*

The ability of + and *Ta* body dermis to induce the development of body hairs in tail epidermis and the ability of tail epidermis to retain its original character

Table 3. *Numbers of wild-type* (+) − *tabby* (Ta) *recombinants incorporating body dermis and either body* (B) *or tail* (T) *epidermis which produced successful grafts and numbers with and without zigzag hairs*

Genotype and regional source epidermis/dermis	Ages of donor embryos (days)	No. successful grafts	No. with zigzags	No. without zigzags
Body/Body				
+B/+B	14/14	6	6	0
+B/TaB	14/14	7	7	0
	13/14	4	4	0
	13/15	3	3	0
TaB/+B	14/14	6	0	6
	14/13	1	0	1
	15/13	8	0	8
TaB/TaB	14/14	10	0	10
Tail/Body				
+T/+B	14/14	4	4	0
+T/TaB	14/14	4	4	0
TaT/+B	14/14	3	0	3
TaT/TaB	14/14	1	0	1

Table 4. *Percentages of zigzags in hair tufts plucked from grafts of body skin explants and from recombinants incorporating either* + *body epidermis* (B) *or* + *tail epidermis* (T) *and* + *or* Ta *body* (B) *dermis*

Genotype and regional source epidermis/dermis	Ages of donor embryos (days)	No. samples counted	% Zigzags (mean ± s.e.)	Range
Explants +	14	6	78·4 ± 3·5	65·0–90·0
Recombinants				
Body/Body				
+B/+B	14/14	6	77·3 ± 4·5	57·6–88·1
+B/TaB	14/14	7	80·3 ± 4·8	60·5–95·0
	13/14	4	64·4 ± 3·0	55·8–69·0
	13/15	3	68·5 ± 7·4	59·0–79·3
Tail/Body				
+T/+B	14/14	4	46·5 ± 16·8	22·5–96·1
+T/TaB	14/14	4	34·9 ± 3·6	25·9–43·4

were tested by preparing the four possible recombinants, i.e. wild-type tail epidermis − wild-type body dermis ($+T/+B$), wild-type tail epidermis–tabby body dermis ($+T/TaB$), tabby tail epidermis–wild-type body dermis ($TaT/+B$) and tabby tail epidermis–tabby body dermis (TaT/TaB). Epidermis and dermis from 14-day old embryos were used in all recombinants.

Successful grafts of all four recombinant types produced body hair rather than tail hair and there were no signs of scale development on the grafts. Like successful recombinants incorporating + body epidermis ($+B/+B$ and $+B/TaB$), successful recombinants incorporating + tail epidermis ($+T/+B$ and $+T/TaB$) produced

zigzag hairs (Table 3). However the proportion of zigzags in the samples from the $+T/+B$ and $+T/TaB$ recombinants was smaller than the proportion in hair samples from $+B/+B$ and $+B/TaB$ recombinants (Table 4). The difference between the mean value for all body epidermis recombinants ($77\cdot3\pm4\cdot5$ S.E.) and all tail epidermis recombinants ($40\cdot7\pm8\cdot2$ S.E.) reached significance ($t = 3\cdot28$, $P < 0\cdot001$). Successful recombinants incorporating tabby tail epidermis ($TaT/+B$ and TaT/TaB), like successful recombinants incorporating tabby body epidermis ($TaB/+B$ and TaB/TaB), produced only tabby-type body hairs (Table 3).

The results of these tail/body recombinants, together with the results of body/tail recombinants, suggest that for these two body regions the origin of the dermis is the major factor determining graft morphology. However the reduction in the proportion of zigzags in hair samples from grafts incorporating wild-type tail epidermis, relative to the proportion in grafts incorporating wild-type body epidermis, suggests that the epidermis may also affect morphology. The results therefore confirm the conclusions of Kollar (1970; 1972). In addition the appearance of body hair on $TaT/+B$ and TaT/TaB grafts, like the appearance of tail hair on tabby tail skin grafts, strongly suggests that the absence of hair on the tails of tabby mice is not due to insensitivity of the tabby epidermis to dermal signals.

(iv) *Recombinants of adjacent pieces of wild-type and tabby body epidermis with body dermis*

The coats of black agouti $Ta/+$ mice are striped. Although both wild-type and tabby-type hairs are present in both the light and dark stripes the proportion of zigzags is higher in samples from the latter (Kindred, 1967). We prepared recombinants in which pieces of wild-type epidermis from albino embryos and pieces of tabby epidermis from coloured embryos were placed adjacent to one another on either wild-type or tabby body dermis in an attempt to determine whether the mingling of hair types in the $Ta/+$ stripes could be explained by interactions between adjacent clones of cells in which either X^+ or X^{Ta} was active. These recombinants produced grafts with both albino and coloured hair (Plate II).

Text-figure 1 illustrates the proportions of zigzags, wild-type awls and tabby awls among the hairs plucked from the centres of the wild-type (unpigmented) and tabby (pigmented) areas and among the unpigmented and pigmented hairs in the sample plucked from the junction between the two. In the wild-type area, zigzags and wild-type awls were the only hair types present (with the exception of one sample which included a few tabby-type hairs). In the tabby area, only tabby-type hairs were present in all eight samples. That is, at the centres of each epidermal patch the morphology of the hair was determined solely by the genotype of the epidermis on which it was found. In the junction samples, too, the genotype of the epidermis appeared to be the primary factor determining hair morphology for, although the proportion of unpigmented zigzags was variable, hairs of this type constituted about 50 % of the unpigmented hairs and tabby-type hairs constituted about 80 % of the pigmented hairs. But in addition to unpigmented zigzags and pigmented tabby hairs, junction samples contained a few pigmented zigzags and a few unpigmented tabby hairs. The proportion of zigzags among the unpigmented hairs (50 %) and the proportion of zigzags among the pigmented hairs (10 %) were
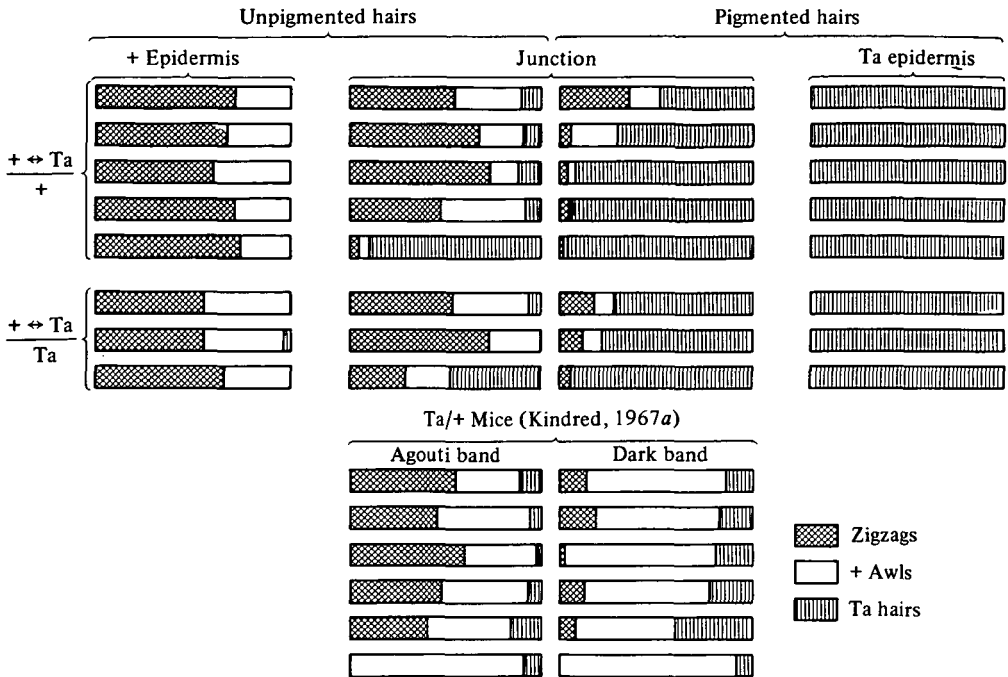
Fig. 1. The proportions of zigzags, wild-type awls, and tabby hairs in samples from the centre of the pigmented (tabby) and unpigmented (wild-type) areas, and in samples from the junction, in recombinants incorporating both wild-type and tabby epidermis on wild-type or tabby dermis, and in samples from the agouti and dark hair coat bands of $Ta/+$ mice (Kindred, 1967).

similar to those observed by Kindred (1967) among hairs from the light (41·7 %) and dark (9·2 %) bands of $Ta/+$ mice.

Like explants and recombinants of tabby tail skin, the morphology of the hairs produced by body epidermis appeared to be affected by contact with epidermis of a foreign genotype. In the case of tail skin explants diffusion of extracellular products between graft and host or in the reverse direction appeared to be the most likely explanation for the fringe of follicles at the graft edge. Diffusion could also explain the appearance of hairs without constrictions on + epidermis and of zigzags on Ta epidermis if the product passing between the two affected the passage of signals from dermis to epidermis. For example, the characteristic alternation of wide and narrow sections in zigzag hairs depends upon changes with time in the proportions of hair follicle bulb cells being channelled into inner root sheath (IRS) and hair (Straile, 1965). If these changes in the numbers of cells channelled into IRS and hair were under dermal control, variations in the ratio of the + and Ta contribution to a diffusible product in the matrix separating dermis from epidermis could perhaps account for the presence or absence of constrictions in the finer hairs produced by the two types of epidermis. However other explanations are also possible, for example cell mingling.

The morphology of body skin explants was less affected by transfer to a foreign host than that of tail skin explants. In recombinants of both body and tail epidermis with body dermis the genotype of the epidermis determined the morphology of the hair produced by the graft, but, when two pieces of epidermis of different genotypes were included in the recombinant, the + epidermis produced a few tabby-type hairs and the *Ta* epidermis produced a few zigzags where the two epidermal types were in contact. The inductive capacity of the dermis and the competence of the epidermis to respond to dermal signals did not appear to vary over the age range of the + and *Ta* embryos used in these experiments (contrast Rawles, 1963).

4. DISCUSSION

The results of the present experiment are in agreement with the findings of both Sofaer (1974) and Mayer & Green (1978); the effect of tabby on the initiation of follicles in tail skin could not be confined to either the epidermis or the dermis (Sofaer, 1974), but the effect of tabby on body hair morphology appeared to be due to activity of the mutant in the epidermis (Mayer & Green, 1978). The explanation for this difference in the site of action with respect to follicle initiation and hair morphology may lie in the difference in the timing of the two events, for follicle initiation occurs between 14 and 21 days post-conception whereas the major period of hair morphogenesis occurs between 20 and 35 days post-conception. The site of manufacture of the product produced by the allele at the *Ta* locus may change with time or the appearance of products produced by other loci at different stages of development may modify its effects.

The result of the experiment in which pieces of wild-type and tabby epidermis were put side by side in combination with body dermis demonstrated that the genotype of the epidermis is the major factor determining hair morphology. However the genotype of the neighbouring epidermis also affected hair morphology at the junction of the two epidermal genotypes. We did not attempt to identify the reason for the appearance of hairs foreign to the epidermal genotype in the junction sample. One possible explanation for the appearance of these foreign hairs may be that a product, affected by the gene at the tabby locus, diffused from the epidermis of one genotype to its neighbour. Various lines of evidence suggest that such a product exists. In *Ta*/+ mice, in which the skin consists of mosaic patches of X^+ and X^{Ta} epidermis and dermis, there is no sign of mosaicism in follicle density on the body or tail (Kindred, 1967; McLaren, Gauld & Bowman, 1973), and the dark and light body hair stripes do not consist of discrete stripes of wild-type and tabby-type hair (Kindred, 1967). McLaren and coworkers (1973) attributed the absence of mosaicism on the tails of *Ta*/+ mice to diffusion of a product between the small patches of X^+ and X^{Ta} skin. In *Ta*/*Ta* – *Ta*/Y mice, follicles fail to develop in tail skin left *in situ*, but explanted tail skin develops follicles (Sofaer, 1974) and these follicles tend to be concentrated at the border of the explant (present results). Sofaer (1974) attributed this increase in the number of follicles initiated in explanted skin to a diffusible product. The gene at the tabby locus, therefore, may prove to share some features in common with *hairless*, for

the gene product produced at this locus, too, is thought to be diffusible (Fraser, 1946).

Grüneberg (1971) and Mayer & Green (1978) suggested that *Ta* may produce its effects by reducing the responsiveness of the epidermis to dermal stimuli. We found that tabby tail epidermis, which produces no follicles or hairs if left *in situ*, was capable of producing as many tail hairs as wild-type tail epidermis when it was combined with wild-type tail dermis, and that it was capable of producing a thick tuft of tabby body hair when combined with either wild-type or tabby body dermis. These results show that, provided conditions are suitable, tabby tail epidermis is capable of producing follicles in response to dermal stimuli. The effect of *Ta* on follicle initiation, therefore, must be mediated via a mechanism other than epidermal sensitivity. The mounting evidence that *Ta* is involved in some way with a diffusible product would suggest that the gene at the *Ta* locus produces a product which diffuses out of the cell, that this product affects the matrix separating the two skin layers and that the matrix in its turn affects the transmission of signals from dermis to epidermis.

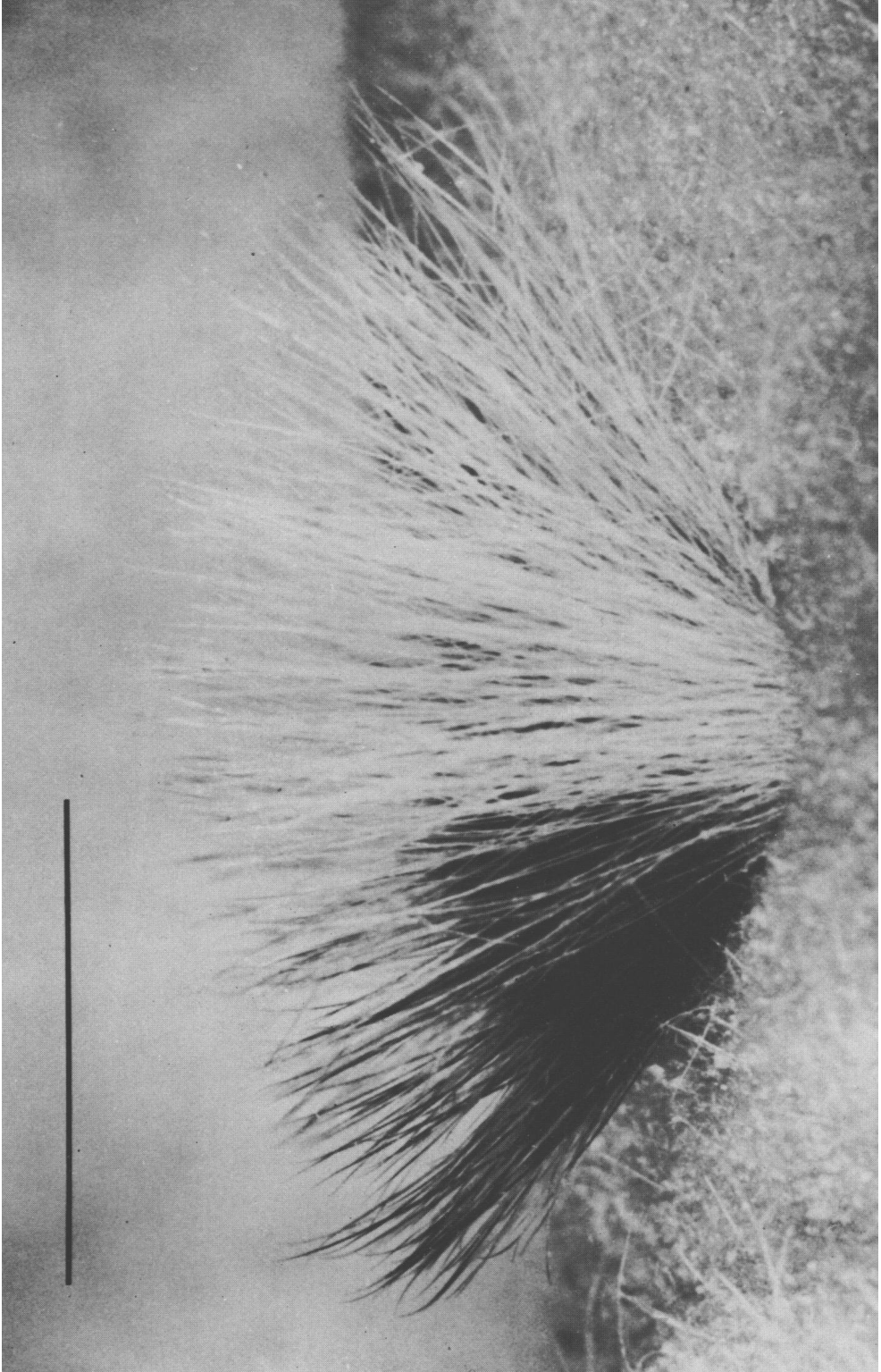## REFERENCES

CLAXTON, J. H. (1966). The hair follicle group in mice. *Anatomical Record* **154**, 195–208.

CLAXTON, J. H. (1967). The initiation and development of the hair follicle population in tabby mice. *Genetical Research* **10**, 161–171.

DRY, F. W. (1926). The coat of the mouse (*Mus musculus*). *Journal of Genetics* **16**, 287–340.

FALCONER, D. S. (1953). Total sex-linkage in the house mouse. *Zeitschrift für Vererbungslehre* **85**, 210–219.

FALCONER, D. S., FRASER, A. S. & KING, J. W. B. (1951). The genetics and development of 'crinkled', a new mutant in the house mouse. *Journal of Genetics* **50**, 324–344.

FRASER, F. C. (1946). The expression and interaction of hereditary factors producing hypotrichosus in the mouse: histology and experimental results. *Canadian Journal of Research Section D Zoological Sciences* **24**, 10–25.

GRÜNEBERG, H. (1969). Threshold phenomena versus cell heredity in the manifestation of sex-linked genes in mammals. *Journal of Embryology and Experimental Morphology* **22**, 145–179.

GRÜNEBERG, H. (1971). The glandular aspects of the tabby syndrome in the mouse. *Journal of Embryology and Experimental Morphology* **25**, 1–19.

KINDRED, B. (1967). Some observations on the skin and hair of tabby mice. *Journal of Heredity* **58**, 197–199.

KOLLAR, E. J. (1970). The induction of hair follicles by embryonic dermal papillae. *Journal of Investigative Dermatology* **55**, 374–378.

KOLLAR, E. J. (1972). The development of the integument: spatial, temporal and phylogenetic factors. *American Zoologist* **12**, 125–135.

MCLAREN, A., GAULD, I. K. & BOWMAN, P. (1973). Comparison between mice chimaeric and heterozygous for the X-linked gene tabby. *Nature (London)* **241**, 180–183.

MAYER, T. C. & GREEN, M. C. (1978). Epidermis is the site of action of tabby (*Ta*) in the mouse. *Genetics* **90**, 125–131.

RAPHAEL, K. A. & PENNYCUIK, P. R. (1980). The site of action of the naked locus (*N*) in the mouse as determined by dermal-epidermal recombinations. *Journal of Embryology and Experimental Morphology* **57**, 143–153.

RAWLES, M. E. (1963). Tissue interactions in scale and feather development as studies in dermal-epidermal recombinations. *Journal of Embryology and Experimental Morphology* **11**, 765–789.
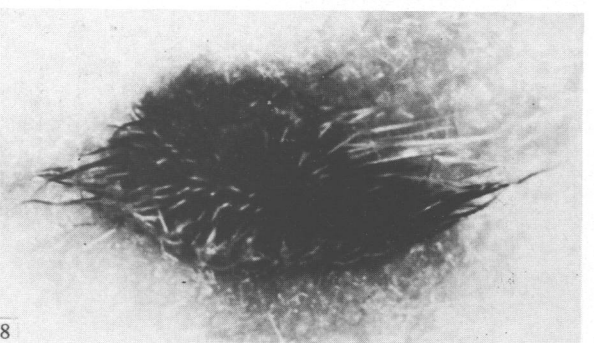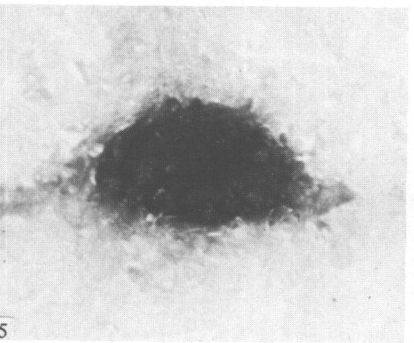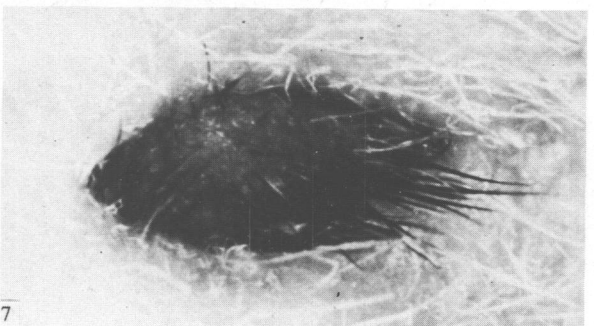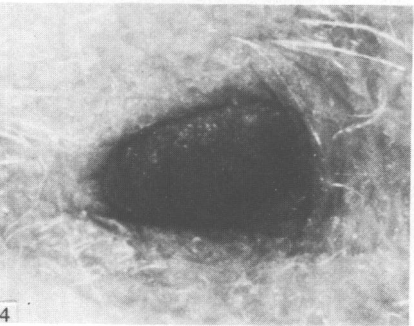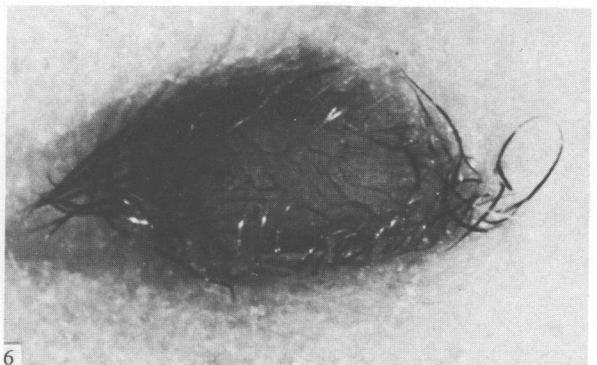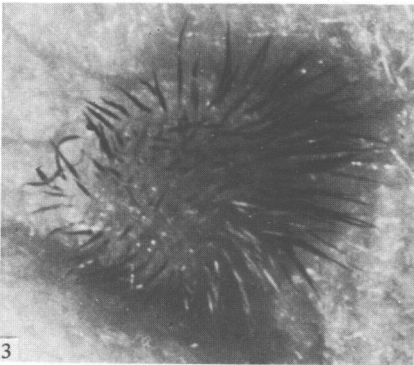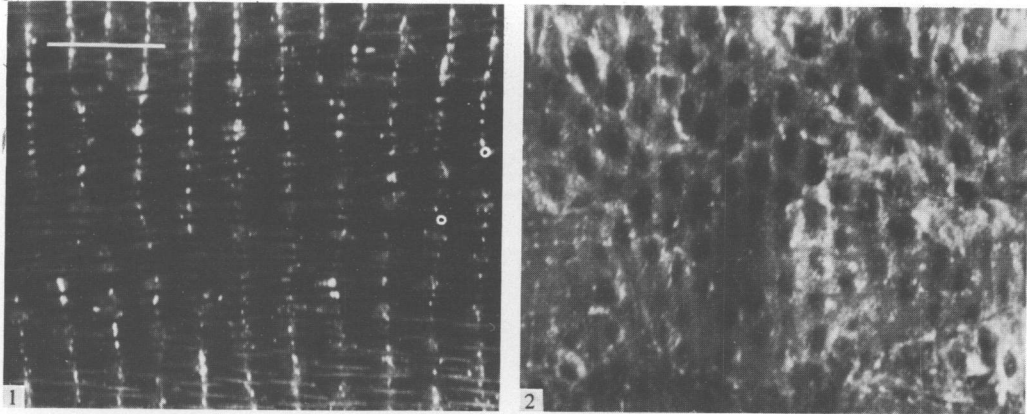
PAMELA R. PENNYCUIK AND KATHRYN A. RAPHAEL
(Facing p. 62)

PAMELA R. PENNYCUIK AND KATHRYN A. RAPHAEL

SOFAER, J. A. (1974). Differences between tabby and downless mouse epidermis and dermis in culture. *Genetical Research* **23**, 219–225.

STRAILE, W. E. (1965). Root sheath-dermal papilla relationships and the control of hair growth. In *Biology of the Skin and Hair Growth*, (ed. A. G. Lyne and B. F. Short), pp. 35–57. Sydney: Angus and Robertson.

EXPLANATION OF PLATES

PLATE 1

Tail skin of wild-type and tabby mice left *in situ* and tail skin of the same developmental age (40 days post-conception) grafted to a nude host. The skin pieces grafted to the nude mice were from 14 or 15-day old embryos (Bar line = 1 mm).

Fig. 1. Tail skin from wild-type mouse.
Fig. 2. Tail skin from tabby mouse.
Fig. 3. Wild-type tail skin graft with an even cover of hair.
Fig. 4. Tabby tail skin graft with pigment but no hair.
Fig. 5. Tabby tail skin graft with an irregular distribution of hair.
Fig. 6. Tabby tail skin graft with hair around the edge.
Fig. 7. Tabby tail skin graft with hair around the edge and a less dense cover in the centre.
Fig. 8. Tabby tail skin graft with an even cover of hair.

PLATE 2

Graft of recombinant in which pieces of tabby body epidermis (from a 14-day pigmented embryo) and wild-type body epidermis (from a 13-day albino embryo) were put side by side in combinations with tabby body dermis. The graft was grown on a nude host for 26 days; the tabby (pigmented) area is on the right, the wild-type area (unpigmented) is on the left. (Bar line = 5 mm).