'Matted', a New Hair-mutant in the House-mouse: Genetics and Morphology

by A. G. SEARLE and R. I. SPEARMAN

From the Medical Research Council Group for Experimental Research in Inherited Diseases, University College London

WITH ONE PLATE

Three types of hereditary hairlessness are known in the house-mouse. With Naked (Fraser, 1946) and Alopecia (Dickie, 1955), baldness results from the breaking of hairs; with hairless and its allele rhino, from the shedding of entire hairs (Fraser, 1946). The crinkled (Falconer, Fraser, & King, 1951) and ragged (Carter & Phillips, 1954) genes, however, lead to a complete absence of certain hair-types, due to delayed or imperfect follicle development (agenesis). In rough (Falconer & Snell, 1952) the fur is greasy and looks unkempt but no baldness occurs.

Matted, the new mutant to be described in this paper, belongs to the first of these three categories. The degree of baldness varies greatly; there may be no signs of any hair loss, or a complete absence of fur over the back and flanks. The head and belly are not affected as a rule. The more extreme manifestation is associated particularly with the later stages of each coat generation. Whatever coat is present it looks and feels rough, in sharp contrast to the sleekness of the normal mouse. Instead of lying down flat against the body, the mutant’s hairs tend to stand up as if inflexible and stick together at the tips so as to form matted clumps; a very characteristic feature (Plate, figs. A, B, C). In agouti mice this erection of the hair causes a darkening of coat colour, for the black basal part of each agouti hair becomes visible.

The present paper deals with the genetics of the new mutant and explains its effect in terms of the underlying abnormalities of hair structure. A paper by Jarrett & Spearman (1957) deals with finer structure and the results of chemical and physical studies.

GENETICS

The matted gene first appeared as a spontaneous mutation in the inbred CBA/Gr strain in 1952. The whole CBA stock was breeding poorly and looking out of condition at the time, but some mice were particularly unkempt, with

1 Authors' address: Department of Genetics, University College London, Gower Street, W.C.1, U.K. A. G. Searle is now at the Department of Zoology, University of Malaya, Singapore.

bald patches on the back. These mice were outcrossed to the C57Bl/Gr strain. All F\textsubscript{1} offspring had normal sleek fur, but about one-quarter of the F\textsubscript{2} were of the matted phenotype (Table 1). Reciprocal backcrosses both gave ratios of matted to normal which did not differ significantly from 1:1, while matted × matted crosses gave only matted offspring. Thus it is clear that this hair abnor-

TABLE 1

\textbf{Segregation data for matted}

<table>
<thead>
<tr>
<th>Father</th>
<th>Mother</th>
<th>Normal</th>
<th>Matted</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>majma</td>
<td>+/+</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>majma</td>
<td>ma/ma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/+</td>
<td>ma/ma</td>
<td>249</td>
<td>80</td>
<td>329</td>
<td>24.3</td>
</tr>
<tr>
<td>majma</td>
<td>+/+</td>
<td>103</td>
<td>91</td>
<td>194</td>
<td>46.9</td>
</tr>
<tr>
<td>+/+</td>
<td>ma/ma</td>
<td>154</td>
<td>132</td>
<td>286</td>
<td>46.2</td>
</tr>
<tr>
<td>ma/ma</td>
<td>ma/ma</td>
<td>0</td>
<td>107</td>
<td>107</td>
<td>100</td>
</tr>
</tbody>
</table>

mality is due to a single fully penetrant recessive autosomal gene for which the symbol \textit{ma} is proposed. There is no evidence of any reduction in viability and fertility is high, many matted mothers having as many as ten litters, while the size of litters is normal. No linkage studies or tests for allelomorphism with other hair genes have yet been made.

The age at which this mutant can first be identified on its external appearance varies between 2 and 4 weeks, being generally somewhat earlier in agouti than in black mice mainly owing to the former’s abnormally dark appearance. Matted mice may appear almost normal with the growth of a new hair generation, but as the hair lengthens the abnormal aspect is regained. If the fur is stroked in the wrong direction the characteristic matted appearance of the hair is more easily seen.

\textbf{MORPHOLOGY}

The external appearance of matted mice differs from normal in showing, (i) erection of hair, (ii) matting of hair in clumps, (iii) a tendency to baldness, (iv) a change to a brown colour of black melanin in old hairs. The explanation of the apparent paradox between this and the darkening of the agouti coat is that the proximal parts of agouti hairs even when changed in colour are darker than the tips.

\textit{Erection of hair}

Hair erection might be caused by inflexibility, or by the angle between epidermis and emerging hair being greater than normal. Flexibility was tested by repeatedly bending a small number of hairs over the edge of a glass slide and watching microscopically for resistance to bending. Only undamaged hairs were used. While normal hairs formed evenly curved bends at the point of stress, with
no sign of splitting, matted hairs bent sharply. Repeated bending of these produced splitting along the cortex (Text-fig. 1). It is clear, therefore, that matted hairs are less flexible than normal ones.

**Text-fig. 1.** Matted awl hair showing a typical sharp bend and splitting at a point of repeated stress. Camera lucida drawing.

Comparisons of the orientations of hair shaft and follicle to the epidermis in normal and matted mice were made from sagittal sections of the skin. A fresh untreated segment of the skin was spread fur uppermost on a dry slide, a thick
section was cut with a sharp blade, moistened, and arranged along the slide edge. By holding the slide vertically under the microscope and viewing by reflected light, the course of several follicles and hairs could be followed without further treatment (Text-fig. 2). The follicle angles of normal and matted hairs show no appreciable difference, but the emergent matted hairs do not curve back against the skin like the more flexible normal hairs.

*Matted clumps of hair*

The largest clumps are seen in the long hair of the back, usually when the coat is thin owing to hair loss. When the coat is thick, fewer hairs are found in each clump, the numerous small clumps giving a rough appearance to the fur.

When individual clumps were examined microscopically they were found to contain all the four hair-types described by Dry (1926). Counts of dorsal and ventral hair-samples gave similar proportions of guard-hairs, zigzags, awls, and auchenes to those for normal mice.

![Text-fig. 3. A matted clump of hairs, stuck together towards their tips. Camera lucida drawing.](image)

Hairs in a clump tend to stick together distally (Text-fig. 3). Normally this adhesion results from the mouse grooming itself, for if the matted coat is brushed and combed free of clumps it is seen that clumping occurs again wherever the mouse licks its coat. This moistened paintbrush effect of surface tension can be simulated in a normal mouse by applying enough water and ruffling the fur, but it is not very noticeable during grooming as the coat is thick and flat against the skin. Observations on normal mice whose coats had been wetted and ruffled showed that clumps remained even after the hair had dried, and only disappeared when the mouse groomed itself, combing and flattening them with its tongue.
The matted mouse, however, cannot smooth down its fur because of the inflexibility of individual hairs; licking its coat therefore merely produces new clumps. The normal salivary mucus seems to help in holding the hairs together. This was suggested by the fact that separation of the hairs from matted clumps occurred after digestion with papain in saline, and to a lesser extent with plain saline, but not with distilled water even on shaking. Matted clumps of hair soaked in ether to remove fat remained stuck together on drying, so sebum is probably not involved. Fibres separated from each other microscopically generally had smooth edges, suggesting that frictional effects due to cortical damage is unimportant in keeping hair stuck together. This also followed from the discovery that if the coat of a normal mouse was well bleached with hydrogen peroxide (20 volumes), the hair became inflexible and erected, with marked clumping at once, before the brittle hairs could have been broken. The next coat generation following treatment was normal.

These facts, together with a detailed microscopic examination of matted clumps, suggest that the inflexibility of the hair is the underlying cause of clumping, while the general tendency of both matted and normal hairs to twist round each other when clumped, and the normal stickiness of the saliva help to keep hairs stuck together.

**Tendency to baldness**

The fact that the hair is inflexible and brittle suggests that breakage is the cause of baldness. Individual hairs were therefore plucked close to the skin and examined. Those from bald areas were often broken, but only minor splitting was seen where the coat was thick. Plucked matted hairs as often as normal retained the follicle bulbs, so tensile strength of fibres is good. It was found that when two very bald mice were placed in separate boxes without food-hoppers they regained a complete hair cover on growth of the next hair generation, although control matted sibs (with metal food-hoppers) stayed bald. Replacing the food-hopper in the experimental cage led to renewed baldness. Loss of dorsal hair is due therefore to friction between the coat and the metal food-hopper. Scratching the flanks may lead to small bald patches.

Individual hairs were examined in detail after passing through absolute alcohol, alcohol + xylene, and xylene (Dry, 1926), then mounting in Canada balsam or distrene. Serial transverse sections of hairs embedded in hard paraffin wax (m.p. 67° C.) were also cut at 10 μ with an ordinary microtome. A Hardy textile fibre microtome (Wildman, 1954) was also used. Measurements with a micrometer of the diameters of awls and zigzags showed no significant difference from normal.

Intact matted hairs do not differ morphologically from normal hairs; the differences become noticeable as a result of mechanical stresses which damage matted hair but do not affect normal hair. During the first few days growth of a new matted coat no hair abnormalities are visible. Slightly later, however,
Splinters of cortical and cuticular keratin can be found partially broken off some fibres. In older hair-samples longitudinal splitting is often very severe; there may be complete breakage of the shaft (Text-figs. 4, 5A). This has been seen in all hair-types except sinus hairs; no particular region of the fibre is affected. Thus zigzags break as often in the middle of a segment as at the constrictions.

At the time when splitting of hairs is first seen, certain regions along the shaft can be found where the accumulations of melanin pigment granules in medullary cells is dispersed or has disappeared entirely. It may be that bending of hairs which is insufficient to cause external breakage can sometimes disrupt medullary cells by compression at the bend, although this phenomenon was not seen in artificially bent hairs. Early in a hair generation hairs are fully pigmented.

The cortical cells of matted hair were examined after digestion for 48 hours in a solution of 2 per cent. papain plus 2 per cent. potassium bisulphite at 37° C. and grinding the digest with a soluble gritty salt, sodium citrate (Lennox, 1952). The spindle-shaped cells thus obtained (Text-fig. 5B) did not differ from those of normal mouse-hair cortex. To separate cells in both cases it was necessary to grind for about 10 minutes with pestle and mortar, so the cement substance does not appear to be weak. Nevertheless, the similarity between the jagged ends of broken matted hairs (Text-fig. 5A) and the spindle-shaped tips of the cortical cells suggests that splitting commonly occurs between cells rather than through them. This could be explained by the cement substance being normal in strength.
and the hair-cells being more rigid and inflexible than normal, so that on bending, splitting occurs at the place relatively weakest, between adjacent cells. Unlike matted, Naked (N/+) hairs examined were found to have cleanly broken ends and did not show much longitudinal splitting.

Matted and normal skin samples from young (2–3 weeks) and adult mice were fixed in aqueous Bouin's solution, sectioned sagittally at 8 μ and stained in Ehrlich's haematoxylin and eosin. No hair breakages were found within matted follicle sheaths and the follicles themselves had well-formed bulbs. Sebaceous glands and other epidermal structures were normally developed. To check follicle density, skin fixed in aqueous Bouin's solution was macerated in warm 5 per cent. acetic acid for 4 hours and the underlying muscle dissected away. This method was modified from Dry (1926). After dehydration and clearing, the skin was mounted flat. Follicle numbers were counted under low power. Those for matted skin were of normal density even in bald areas.

Change in hair colour

The coat of a genotypically black-matted mouse tends to become russet in colour in old hairs. This change occurs even in the dark and affects the individual melanin granules which become translucent and brown (Plate, figs. D, E); hence it is not just the result of loss of melanin due to damage. The change in black melanin seems to result from the speeding up of a normal ageing process, for there is a tendency for some normal C57 black mice to become browner at the end of a coat generation, and this is also caused by an alteration in individual granules.

DISCUSSION

We have shown that the matted phenotype is due to a recessive gene which alters the mechanical properties of the hair. Hairs become inflexible and brittle, tending to split longitudinally and break off when bent. When compared with other hair genes in the mouse the action of matted shows clear similarities with that of Naked described by David (1932, 1934) and Fraser (1946), and Alopecia (Dickie, 1955), in that baldness results from the breakage of hairs above the skin and not from hairs falling out through malformed follicle end-bulbs, or from agenesis, but the threshold for breakage is much higher in matted than in these two mutants; environmental conditions therefore assume much greater importance in determining phenotypic appearance. This difference in threshold is well brought out by the time taken for baldness to develop: hair-loss is generally complete in a week in Naked N/+ mice, but may not occur at all in matted. For this reason a sharp demarcation between hairy and bald areas is rarely seen in matted mice.

In Naked mice some of the first-formed hairs fail to penetrate the epidermis and remain coiled in the follicles. This phenomenon has not been found in matted hairs, which are brittle rather than soft. The matted gene agrees with
Naked N/+ in not affecting the sinus hairs, or general skin histology. Matted skin is not abnormally thickened or folded. In both Alopecia and Naked, scattered guard-hairs remain on otherwise bald areas, whereas in matted all types of hairs are equally affected and show breakage.

The matted type of hair-breakage with longitudinal splitting occurs as a rare abnormality in many mammals. In human trichorrhexis nodosa (Ormsby & Montgomery, 1954) the hairs are brittle and resemble matted in having good tensile strength. The severity of the defect varies, but typically affected hair remains short and looks rough as in matted mice. A change in hair colour has not been noticed. Although this abnormality has been recognized for well over a century its cause is still obscure, and while a similar complaint in horses is apparently an infection (Král & Novak, 1953) this seems not to be the case with the human disease. Hydrogen peroxide, which on normal mouse-hair gives a phenocopy of matted, can lead to trichorrhexis nodosa in human hair if used in excess.

The premature ‘ageing’ of melanin granules in matted is probably related to abnormal keratin formation, as the production of both is known to be interconnected. Thus Rauch (1952) has shown that in the rat avidin poisoning from a diet of raw egg albumen (the so-called biotin deficiency) results in dermatitis, hair brittleness and breakage, and abnormally light pigmentation. Tyrosine is a precursor of melanin and an important constituent of keratin and the blocking of certain enzyme syntheses is likely to affect both keratinization and melanin production. Tyrosinase is activated by copper, and Lerner & Fitzpatrick (1950) and others have shown that substances which remove free copper ions tend to reduce pigmentation by inactivation of this enzyme. Copper is also active at some stage in keratinization and the connexion is exemplified by the ‘falling disease’ in sheep fed on copper deficient pastures; Marston & Lee (1948) finding abnormal wool formation as well as more serious effects. Matted seems to differ from these conditions since melanin when first formed seems normal, but possibly it is unstable chemically. According to Baker & Andrews (1944) red melanin is an oxidation product of black melanin. When normal black mice are lightly bleached with hydrogen peroxide the russet colour produced resembles that seen in matted hair. Possibly the extensive colour change in old matted hair as well as the less-marked change in normal black hair result from oxidation of melanins differing in stability. Since all mice were kept in semi-darkness bleaching by light was not involved. The colour change is confined to the cortical and medullary melanin granules described by Russell (1949) and no change is seen in keratin in melanin-free places.

We can see then that the effect of the matted gene on the hair-fibres themselves, and on the pigment they contain both suggest that it interferes fundamentally with normal keratin formation, leading to what can be vaguely termed ‘a defect in keratinization’. Studies on the keratin abnormality are described in another paper (Jarrett & Spearman, 1957).
A NEW HAIR-MUTANT IN THE MOUSE

SUMMARY

1. Matted (symbol ma) is a fully penetrant recessive mutant in the house-mouse which does not reduce fertility or viability under laboratory conditions.

2. It affects the coat, producing: (i) erection of the hairs, with the formation of matted clumps of hair, giving it an unkempt appearance; (ii) a variable amount of baldness, depending on areas of friction and resultant hair breakage; (iii) a colour change to russet which happens regularly towards the end of each hair regeneration in black hair.

3. The hairs are inflexible and brittle, tending to split longitudinally when bent. Medullary pigment granules are lost over short lengths of the hair, presumably because of breaks in the keratin. Tensile strength is normal.

4. Prolonged application of hydrogen peroxide to the normal mouse coat produces a phenocopy of matted which persists until the next hair generation is formed.

5. Similar conditions in mouse and man are discussed, and possible connexions between the abnormal keratinization and the change in hair colour.

ACKNOWLEDGEMENTS

We are grateful to Prof. H. Grünberg, F.R.S., for the interest he has shown in this work. We also wish to thank Prof. E. Baldwin and Dr. N. Barnicot for advice and criticism. Mr. R. Lees kindly helped with photography and the manuscript was typed by Miss H. Bartels.

REFERENCES


RUSSELL, E. S. (1949). A quantitative histological study of the pigment found in the coat colour mutants of the house-mouse IV. *Genetics,* 34, 146–66.


**EXPLANATION OF PLATE**

**Fig. A.** Normal agouti mouse.

**Fig. B.** Matted agouti mouse showing the rough appearance of the coat with erection and clumping of the inflexible hair.

**Fig. C.** Matted black mouse with more pronounced clumping of hairs than in Fig. B. A bald patch is just visible on the back near the shoulders. This mouse had previously been completely bald on the back.

**Fig. D.** Pigment granules in normal black mouse-hair. The size of medullary pigment cells varies greatly. ×875. Cleaned Canada balsam preparation.

**Fig. E.** Pigment granules in an old matted black hair. Granules in the medullary cells are beginning to separate and individual granules have changed from black to brown in both medulla and cortex. ×875. Cleared Canada balsam preparation.

*Manuscript received 25: vi: 56*