More about the tabby mouse and about the Lyon hypothesis

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INTRODUCTION

Autosomal genes are present in duplicate in the body cells of both sexes. Genes carried in the X-chromosome are present in double dose in the mammalian female, but only in single dose in the mammalian male. Despite this disparity in gene dosage, the phenotypic effects of such genes are generally the same in homozygous and in hemizygous condition. To bring about this situation, some kind of 'dosage compensation' is required. A possible mechanism of dosage compensation in mammals which has been widely discussed in recent years is the 'inactive-X-chromosome' or 'single-active X-chromosome' hypothesis. As originally put forward by Lyon (1961, 1962), this postulates that during embryonic development, either the maternal or the paternal X-chromosome of the female is inactivated. Inactivation happens at random and is irreversible; it thus persists in the descendants of the cell in which it has occurred. The mammalian female, according to this hypothesis, is thus a patchwork mosaic so far as its X-borne genes are concerned, and as in any one cell only one of the two X-chromosomes is active, the effective dosage is the same in both sexes.

The observational starting-point of the hypothesis was the fact that heterozygotes for several sex-linked genes in the mouse and other mammals show what appears to be, or could be interpreted as, a patchwork phenotype, the tortoiseshell cat being the most striking and widely known example. However, a prima facie case in favour of a hypothesis must not be mistaken for a proof. A test of validity will have to establish whether the facts claimed to support the hypothesis are indeed in quantitative agreement with its consequences. Methodologically it is obvious that in the first instance this will have to be done in the simplest genetic situations, taking one gene at a time and studying its behaviour in a structurally normal X-chromosome. Only on the basis of such studies can genetically more complex situations (double heterozygotes, and genes carried in structurally abnormal chromosomes) be critically evaluated.

It is surprising that, whereas there are many data involving complex situations, there is very little information as to whether the individual genes conform to the

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Lyon hypothesis (or L.H. for short). The gene for tabby in the mouse (Falconer, 1953) affects the fur and the teeth (Grüneberg, 1965), and it has been shown recently (Grüneberg, 1966b) that the dental syndrome of Ta/+ ♀♀ cannot be accounted for in terms of the L.H. In this paper, evidence will be presented that this is equally true of the effects of tabby on fur and skin. A survey of the other sex-linked genes in the mouse and other mammals (other than man) will show that, in so far as they provide evidence at all, this evidence is uniformly against the L.H.

No attempt will be made in this paper to deal with complex situations involving the simultaneous segregation of several sex-linked genes or the behaviour of genes carried in structurally abnormal chromosomes; with data from human genetics; or with the cytological aspects of the hypothesis. The possibility thus remains that valid evidence in favour of the hypothesis may come from sources of information not discussed in this paper. It is hoped to come back to an assessment of the remainder of the evidence on a later occasion.

CRITERIA FOR TESTING THE VALIDITY OF THE LYON HYPOTHESIS

A test of the L.H. will, in the first instance, have to establish whether individual sex-linked genes, in structurally normal chromosomes, behave according to expectation in heterozygous females. Some of the criteria for this simple situation have been discussed in a previous paper (Grüneberg, 1966b); others will be added here. No doubt the list is still not complete.

1. To establish critically whether the phenotype of a heterozygote is in agreement with the L.H., the phenotype of both hemizygotes must be known, as, for example, in tabby. In the mottled series of (probable) alleles, the fur of brindled (Mo$^{br}$) ♀♂ is affected uniformly all over, and it may reasonably be supposed that this would also be true for other alleles like mottled (Mo) or dappled (Mo$^{dp}$) if the ♀♂ lived to grow fur. On the other hand, the phenotype of the lethal striated (Str) ♀♂ is of necessity conjectural.

2. Where an organ or structure is affected in its entirety in the hemizygote (such as fur and molars in Ta or the fur in Mo$^{br}$ ♀♂), the patches of normal and mutant phenotype in the heterozygote, on the L.H., must be arranged at random. The existence of an orderly arrangement (pattern) is quite incompatible with that hypothesis, as random inactivation of chromosomes cannot generate an orderly (i.e. non-random) pattern. Patterns may be recognizable by inspection, or demonstrated statistically by unequal involvement of, or correlations between, different parts of the body.

3. Where the phenotype of the hemizygote is itself a pattern (as in bent-tail (Bn) ♀♂), the emergence of a similar pattern in the heterozygote is equally compatible with the L.H. and conventional semi-dominance and thus does not discriminate between these alternatives.

4. Clearly demarcated patches of normal and mutant phenotype in heterozy-
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gotes should show the respective phenotypes pure and uncontaminated, and no intermediacy. This, of course, depends on autonomous development (without which clearly defined patches could not be formed), and on the absence or near-absence of mingling of cells of contrasted type. The latter should be the case near the middle of large patches.

(5) As a corollary to (4), the regular occurrence of large areas of uniformly intermediate phenotype in heterozygotes is incompatible with the L.H., as in such areas both alleles must be at work together, as in ordinary (autosomal) heterozygotes.

(6) The contrasted patches, to fit the L.H., should on an average cover equal areas in the aggregate. This again depends on autonomous development and on equal growth of the respective sectors following the inactivation of the paternal and maternal X-chromosomes respectively. As I have pointed out elsewhere (Grüneberg, 1966b), ‘in a genetically heterogeneous strain [differential growth], if it should occur, would also be influenced by other sex-linked genes which, in relation to A/a, would be in coupling and repulsion at random and thus act as a buffer’. Moreover, as any appreciable differential growth of sectors would inevitably lead to gross malformations, it is improbable that any major disparity in the aggregate area of contrasted sectors can be explained in terms of differential growth.

(7) According to the L.H., paternal and maternal X-chromosomes are inactivated at random, i.e. regardless of the genes they carry. If so, the manifestation of contrasted alleles in heterozygotes should be refractory to selection. Successful selection for or against the manifestation of alleles in heterozygotes would demonstrate genetic (Fisherian) control of dominance at the level of the gene. Selection for a gene, of course, always involves adjacent regions of the chromosome and sometimes the whole of it, but not the propensity of the opposite chromosome to be inactivated (if, for example, in a heterozygote A/a, one can select for increased manifestation of A, this would, in terms of the L.H., involve increased inactivation of the chromosome carrying a, and vice versa). Random chromosome inactivation, ex hypothesi, involves absence of any control and hence failure to respond to selection.

(8) If the heterozygote for an autosomal gene shows ‘mosaic’ manifestation, this must be interpreted in terms of ordinary semi-dominance in conjunction with a threshold mechanism. If a sex-linked mimic of such a gene behaves in the same way, the parsimony principle militates against invoking a totally different interpretation for the same phenomenon.

Throughout, the above criteria either contradict the L.H., or they fail to discriminate. Thus, existence of a pattern is incompatible with the hypothesis, but absence of a pattern is equally compatible with the L.H. and with ordinary semi-dominance, and similarly for all the other criteria.
THE COAT OF THE NORMAL MOUSE

The coat of the normal mouse has been studied by Dry (1926), Fraser (1951) and Slee (1957). In the mid-dorsal region, Dry distinguishes four types of hairs, with very few intermediates. The overhair includes three coarse types of fibres (guard-hairs, awls and auchenes, respectively) which together in Dry's mice accounted for about 16% and in Fraser and Slee's animals for about 28% of all the hairs of the baby coat. The remainder consists of fine fibres (zigzag hairs) which form the underfur. Dry (1926) found that 1627/2000 hair follicles produced the same kind of fibre in the first and second hair generation; in 362 follicles (18.1%), a finer hair was succeeded by a coarser one (mainly auchenes by awls (137) and zigzags by auchenes (174 cases)), and only in 11 instances was a stronger hair replaced by a thinner one. Dry used mainly three criteria for the classification of the four hair types. Guard-hairs (which are the longest fibres) and awls lack constrictions, auchenes have one constriction and zigzags from 3 to 5, with angulations at each (hence the name). Medullary pigment is present in the transverse septa (complete partitions) or in columns of septules (incomplete partitions) the latter of which only occur in the overhairs. The internal structure of the medulla is a function of hair calibre. Thus the fine zigzag hairs (with maximum diameters of 14-15 μ) are septate throughout except at the constrictions where the medulla may be interrupted. The overhairs, in the thicker middle regions, have rows of septules (2 in guard-hairs, and up to 5 in the strongest awls of adult mice); but near the tip and near the base where they are thin, the overhairs are also septate. The change of calibre is steady, and the transition from septate to septulate and back again to septate near the base happens within a few partitions and generally without uncertainty and hesitation. Guard-hairs have a longer solid tip than the other hair types and lack the yellow agouti band which is present in nearly all the other hairs; they are roughly circular in cross-section whereas awls are bean-shaped.

In the normal mouse, the four hair types distinguished by Dry can easily be sorted out under the dissecting microscope, mainly on the basis of the constrictions. But this method breaks down completely in a coat which includes anomalous hair types. Here it becomes necessary to scan each hair from one end to the other under the medium or high power of the microscope, a procedure as tedious as it is essential for the discovery of smaller deviations from normality. As this inevitably restricts the size of the hair sample which can be examined, some authors have preferred to classify a large sample of hairs superficially under the dissecting microscope rather than to scrutinize a small sample in detail under the microscope. This has led to important features in several mutants being overlooked and severely restricts the critical value of these earlier enumerations.
THE COAT OF THE TABBY MOUSE

Historically, the structure and development of the coat of the crinkled \((cr/cr)\) mouse was described first (Falconer, Fraser & King, 1951). The structure of the tabby coat was found to be indistinguishable from that of crinkled, and its development was presumed to be the same (Falconer, 1953). Tabby hemizygotes and homozygotes have a darker coloration along the mid-dorsum than normal mice. By contrast, the remainder of the hairs has a wider band of phaeomelanin so that the fur looks yellower than that of a normal mouse. Typical guard-hairs are absent in the tabby mouse whose coat is short and rather thin. There are no hairs with constrictions. The hairs of tabbies are on an average considerably finer, and the strongest fibres do not exceed 22 \(\mu\) in diameter. The stronger fibres in the tabby coat have an abnormal internal structure, with irregular sequences of septa and septules, i.e. complete and incomplete partitions. There is a conspicuous bald patch behind the ear, and the tail is usually completely naked though occasionally a few hairs are present.

This situation can be accounted for in two different ways. Either the abnormality of the tabby coat is a failure of differentiation; i.e. the fur corresponds to the whole of the normal pelage but lacks its differentiation into guard-hairs, awls, auchenes and zigzags; or certain hair types are absent in the tabbies, namely the long guard-hairs and the hairs with constrictions (zigzags and auchenes), with the result that the tabby fur corresponds to the awls only. These, in the normal baby coat, are about 15-20 \% of all hairs. Falconer et al. (1951) did not succeed in getting a direct estimate of hair density, but decided in favour of the 'awls-only' hypothesis in view of the obvious thinness of the coat together with embryological evidence for which the reader may be referred to the original paper.

The present author has succeeded in getting direct estimates of follicle density in normal and tabby mice. To avoid shrinkage and distortion, the dorsal skin was fixed \textit{in situ} by subcutaneous injection of Bouin's fluid; during the process of fixation, the mouse was put on its back and weighted down slightly to flatten the dorsal skin. The rectangular piece of skin subsequently removed was then dehydrated and cleared in methyl salicylate. The anagen phase of the first and second hair generation was studied. The formation of follicles, in the normal mouse, ceases towards the end of the first week after birth. Thereafter, the follicles spread out as the mouse grows. To make animals of different size comparable with each other, a correction is necessary; in Table 1, the original counts (covering an area of 5-12 mm\(^2\)) are thus given along with adjusted values of hair density which would have been found if the mouse had reached a weight of 20 g; i.e. the original count of each mouse has been multiplied by \((W/20)\) where \(W\) is the weight of the animal. If in the baby coat of the normal mouse (14 days) the proportion of awls were as high as 25 \% (which is certainly an overestimate), the (adjusted) number of hairs expected in tabbies

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on the ‘awls-only’ hypothesis would be 97 whereas 246 were actually observed. The ‘awls-only’ hypothesis is thus untenable. As, in the second hair generation (31 days), the hair density of the tabby is not far from normal, the reduced hair count of tabbies in the first hair generation is probably largely due to retardation, not all hair follicles being active or perhaps even formed. In the light of these data a detailed study of the development of the tabby fur is desirable. In any case, it is obvious that the fur anomaly of tabbies is mainly a failure of differentiation with reduction in hair calibre rather than of hair number. Microscopic examination indeed suggests that tabby hairs are not a homogeneous population as one should expect if they were all (atypical) awls. In the absence of constrictions, a sharp distinction between overhairs and underfur is not possible. Hair calibre in general is much reduced. The finer fibres (believed to be the equivalents of zigzags) usually have a maximum diameter of 10–11 μ (normal 14–15 μ); they are essentially septate, but often have a few short and irregular septulate regions. The absence of constrictions may be a consequence of their reduced calibre. The stronger fibres are usually septate for long stretches at both ends, only the middle region being irregularly septate; evidently, even the thicker parts of the fibre only just reach the threshold at which septation turns into septulation. A minority of the stronger hairs corresponds to fine (2-septulate) awls.

As Falconer et al. (1951) have pointed out, in the normal mouse the tuft of hair behind the ear consists entirely of zigzags. However, these are finer than zigzags elsewhere, have a longer solid tip and generally a long non-medullated base. I am inclined to think that they are absent in tabbies not because they are zigzags, but because they are the finest hairs and thus the first to be pushed over the brink in the general reduction of hair calibre. A similar but diffuse reduction of the finer zigzags is probably present elsewhere in the coat. Incidentally, the bald patch behind the ear in tabbies is a good deal larger than the area occupied by the tuft of zigzags in normal mice.

Table 1. Mid-dorsal hair counts in tabbies and normal litter mates

<table>
<thead>
<tr>
<th>Age</th>
<th>Ta δδ</th>
<th>+ δδ</th>
<th>Ta δδ</th>
<th>+ δδ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight</td>
<td>Hair count</td>
<td>Hair count (adjusted)</td>
<td>Weight</td>
</tr>
<tr>
<td>14</td>
<td>4-91</td>
<td>571</td>
<td>223-9</td>
<td>5-58</td>
</tr>
<tr>
<td></td>
<td>4-94</td>
<td>683</td>
<td>268-9</td>
<td>7-04</td>
</tr>
<tr>
<td>Mean</td>
<td>—</td>
<td>246-4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>31</td>
<td>12-12</td>
<td>453</td>
<td>324-4</td>
<td>19-67</td>
</tr>
<tr>
<td></td>
<td>15-82</td>
<td>—</td>
<td>—</td>
<td>31-9</td>
</tr>
</tbody>
</table>
THE COAT OF TABBY HETEROZYGOTES

The coat of $Ta/+ \, \varnothing \, \varnothing$ has characteristic transverse stripes of black hair which lack the agouti band. They are most obvious in the baby coat and tend to become less marked in the adult animal. Somewhat surprisingly, Lyon and her collaborators have referred to the tabby markings as ‘variegation’. That term is defined in the Concise Oxford Dictionary (4th ed., 1950) as ‘being marked with irregular patches of different colours’ and thus clearly cannot be used legitimately to describe the regular transverse pattern of the $Ta/+ \, \text{mouse}$. The arrangement of the stripes is unmistakably orderly, and orderly patterns are not the result of random events. Moreover, the change of the tabby markings with age is quite alien to the L.H., and the average area covered by the black stripes is far less than one half of the whole coat which would be expected on that hypothesis.

Whereas orderly stripes cannot conceivably be generated by random events, they can easily be accounted for by transverse structures in the developing skin. A slight transverse wrinkling of the skin on the flanks first appears in 15-day embryos (Grüneberg, 1943) and soon becomes very marked (Plate 1, fig. 1). During the growth of the baby fur and again, to a lesser extent, during that of the second hair generation, the skin of the mouse shows marked transverse folds (David, 1934) which are hidden under the fur and which follow approximately the transverse structure of the skin which arises in the 15- to 16-day embryo. Position and size of these folds and their relation to the hair growth cycles suggest that they are the structural features which underlie the transverse markings of $Ta/+ \, \varnothing \, \varnothing$ (and perhaps similarly in other mammals). The coarser pattern of skin folds during the growth of the first coat explains why the tabby markings are most striking in the baby coat. It also accounts for the fact that the face of $Ta/+ \, \varnothing \, \varnothing$ does not show stripes; according to the L.H. there is no reason why it should be immune.

Kindred (1967) rightly remarks that ‘Tabby does not fit into this scheme [the L.H.] very well even on a superficial examination since the dark stripes are equated to the mutant which is, in most parts, more intensely agouti [i.e. has wider yellow bands] than normal’. In fact, the fur composition of the black stripes differs from that of $Ta$ by the presence of guard-hairs (Falconer, 1953; Lyon, 1963; Kindred, 1967) and of some zigzags (Lyon, 1963; Kindred, 1967),

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**Plate 1**

Fig. 1. Normal mouse embryo, 16 days old, showing the transverse wrinkling of the skin which is believed to underlie the transverse stripes in $Ta/+ \, \text{and probably Str/+ } \varnothing \varnothing$.

Figs. 2–4. Tail skin of a normal $\delta$, a $Ta/+ \, \varnothing$ and a $Ta \, \delta$ (49, 65 and 47 days old; tail lengths 91, 91 and 76 mm respectively). The central 3 cm of each tail are shown. This represents the middle third in the first two mice; the corresponding region in the $Ta \, \delta$ is indicated by the arrows. Approximate tail-ring number in the middle third 54, 65 and 70 respectively. The tail skin of the first two mice is shown from the inside as the scale pattern on the outside is partly obscured by hairs.

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neither of which should be present. On the other hand, the intervening agouti areas differ from the normal fur by a reduction in number of (segmented) zigzags (Lyon, 1963; Kindred, 1967); the latter author found 50.9% where some 75–80% would have been expected. Of course one can try to save the L.H. by making ad hoc assumptions such as that the development of guard-hairs (unlike that of other hair types) is non-autonomous, or that the areas sampled were not, in fact, pure (though Kindred, and no doubt Lyon also, took pains to avoid this source of error). Past enumerations of hair types suffer from the fact that under the dissecting microscope little can be seen beyond the presence or absence of constrictions and of the yellow subterminal band. Microscopic examination shows that some of the hairs in agouti areas of Ta/+ ♀♀ correspond to the finer fibres of Ta ♂♂ which are probably unsegmented zigzags; these would be misclassified at low magnifications as awls. Pending a more detailed investigation, the most probable interpretation of the Taj coat is that stripes and agouti areas differ in degree rather than in kind, and that, as in the tail rings (see below), the effects of both alleles are detectable over the whole area of the coat.

The orderly arrangement of the stripes in Ta/+ ♀♀ is obvious to the eye. The existence of a pattern is further demonstrated by a negative correlation between striping and vibrissa number (see next section); the more nearly normal the total number of vibrissae, the less intense the striping, and vice versa (Dun, 1959). The manifestation of the gene in the face (vibrissae) is thus not independent of that on the back (stripes) and hence involves a pattern.

As shown by Fraser & Kindred (1962, and earlier papers), the vibrissa number in Ta/+ ♀♀ responds to selection (a behaviour which in itself is quite incompatible with the L.H.). Dun & Fraser (1959) also found that selection for vibrissa number indirectly affects the degree of striping. Thus in the upwards selection line in which vibrissa number approached normal the stripes tended to disappear, whereas in the downwards selection line they became strikingly more marked—again clear evidence for the existence of a pattern. The genetic background of these selection lines acted specifically on Ta. Kindred (1967) crossed dappled (Mo^dp) and brindled (Mo^br) on to the background of the high vibrissa selection line, but observed no effect on the phenotype of these genes.

**THE SINUS HAIRS (VIBRISSAE)**

The sensory or sinus hairs of the face of the mouse include the mystacial vibrissae (whiskers) which are not appreciably affected by Ta, and certain groups of secondary vibrissae. In the normal mouse, these are almost completely invariant in number. On each side, there are two supraorbital, one postorbital and two postoral vibrissae, and near the midline under the chin there is a group of three inter-ramals. The total number is thus 13. Ta reduces some of these sinus hairs slightly and others strikingly (Table 2). For the group of secondary
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vibrissae as a whole, $Ta/+$ is about intermediate. But the situation is different for individual locations. The gene is dominant for the supraorbitals which are only slightly affected, but almost recessive for the postorbitals which are considerably reduced. In the two remaining groups, the gene is more nearly dominant. Contrary to what one should expect on the L.H., the heterozygous manifestation of tabby as regards the secondary vibrissae thus again shows a pattern, favouring some bristles and avoiding others. The situation is thus similar to that in the molars (Grüneberg, 1966b), where heterozygous manifestation favours $m_2$ as compared with $m_1$.

Table 2. Secondary vibrissae in normal and tabby mice (after Fraser, Nay & Kindred, 1959)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Supra-orbitals</th>
<th>Post-orbitals</th>
<th>Post-orals</th>
<th>Inter-ramals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ $\delta\delta$, +/+ $\varphi\varphi$</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>$Ta/+ \varphi\varphi$</td>
<td>3.7</td>
<td>1.8</td>
<td>2.2</td>
<td>1.6</td>
<td>9.4</td>
</tr>
<tr>
<td>$Ta\delta\delta$</td>
<td>3.7</td>
<td>0.3</td>
<td>1.5</td>
<td>1.2</td>
<td>6.7</td>
</tr>
<tr>
<td>$Ta/Ta \varphi\varphi$</td>
<td>3.8</td>
<td>0.4</td>
<td>1.5</td>
<td>1.2</td>
<td>6.8</td>
</tr>
</tbody>
</table>

TAIL RINGS

The tail of the mouse is covered with scales which are arranged in fairly regular rings, with rows of stiff hairs in the intervals between the rings. The tail of crinkled mice lacks hairs and is thus usually entirely naked, and tail rings are absent from most crinkled mice (Falconer et al. 1951). The same is the case in tabby where the tail is ‘nearly always quite devoid of hair and tail-rings’ (Falconer, 1953).

A closer study of the flat tail skin mounted between glass plates shows that our tabby mice usually have some scales; the amount is variable and the distribution sometimes patchy, and particularly the ventral surface of the tail is often smooth. The scales of tabby mice are much smaller than those of normals (Plate 1, fig. 4), and their arrangement in rings is less regular. The large scales of normal mice are roughly rectangular in outline, and the interval between adjacent scales in the row is narrower than that between successive rows. The scales of tabbies are separated from their neighbours to the right and left by wider intervals, and the whole arrangement of the scales is distinctly hexagonal as in a honeycomb. The number of scales in a row is about the same in normals and tabbies. The scales of $Ta/+ \varphi\varphi$ are uniformly intermediate in size between those of $+ \delta\delta$ and $Ta \delta\delta$ (Plate 1); their arrangement in rings is about as regular as in a normal mouse, but as the rings are narrower, there are more of them per unit length of tail. This is detectable by inspection (Plate 1) where there are about 54, 65 and 70 rings in the middle third of the tail in a $+ \delta$, a $Ta/+ \varphi$ and a $Ta \delta$ respectively. Counts of tail rings are approximate only on account of irregularities; to
minimize the error, the mean of three counts (one near the midline and two near the sides) was taken and recorded to the nearest integer. The counts may be regarded as accurate to within $\pm 1$ ring. The sample examined included 20 normal mice ($19\delta\delta$, $1\varphi$) and 23 $Ta/+\varphi\varphi$ from the same matings; the mean tail length of the normals was 90.05 mm and that of the $Ta/+\varphi\varphi$ 89.00 mm, with almost identical ranges around the mean. The rings have been counted in each case in the 4th and 6th cm, counting from the base of the tail (Table 3). In both segments, the $Ta/+\varphi\varphi$ have significantly more (i.e. narrower) rings than the normal mice; the ratio of tail ring numbers ($Ta/+\delta\delta$ divided by normal) is about the same in both segments (1.160 and 1.127, respectively). No attempt has been made to obtain similar counts for tabbies, as the distribution of scales is too irregular; it is, however, obvious by inspection that their scales are much smaller than those of normals.

| Table 3. Number of tail rings in the 4th and 6th cm of the tail (upper and lower half of the table, respectively) in normal and $Ta/+\delta\delta$ mice |
|---|---|---|---|---|---|---|---|---|---|---|
| Normal | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | Total | Mean |
| $Ta/+\delta\delta$ | 2 | 8 | 7 | 3 | — | — | — | — | — | 20 | 18.55 |
| Normal | — | — | 4 | 2 | 4 | 5 | 7 | 1 | — | 23 | 21.52 |
| $Ta/+\varphi\varphi$ | — | 1 | 6 | 5 | 4 | 3 | 1 | — | — | 20 | 20.25 |
| Normal | — | 1 | 1 | 2 | 5 | 6 | 4 | 4 | — | 23 | 22.83 |

The comparison between normal and $Ta/+\delta\delta$ mice is complicated by the fact that nearly all the normals are $\delta\delta$ whereas the $Ta/+\delta\delta$ mice are all $\varphi\varphi$. A comparison between 10 $\delta\delta$ and 10 $\varphi\varphi$ from a normal stock showed no sign of a sex difference in either segment of the tail, in conformity with the findings of Fortuyn (1939 and earlier papers).

The scale size of $Ta/+\varphi\varphi$ is uniformly intermediate over the whole area of the tail, without any sign of patchiness such as would be expected on the L.H; and individual $Ta/+\varphi\varphi$ are similar in this respect. Evidently, both alleles are interacting with each other as in an ordinary autosomal heterozygote. The situation is probably the same as in the coat where the influence of both alleles was detectable both in the stripes and in the intervening agouti areas (though in that case the possibility of a mingling of contrasted types of hairs has not yet been excluded critically).

There are several probable recurrences of $Ta$ and at least one distinguishable new allele ($Ta'$; Stevens, 1963) whose tail is not naked: ‘They have fewer hairs on the tail than normal, and the hairs are curved. $TaTa'$ $\varphi\varphi$ have hairless areas and areas of curved hairs as would be expected on the basis of the inactive-$X$ theory of Lyon.’ In the absence of detailed critical data, I am inclined to treat this declaration of faith in the L.H. with some reserve.

We mention here another sex-linked gene, greasy ($Gs$; Larsen, 1964) which has not yet been described in detail. It is very closely linked to, but not allelic
with, \( Ta \). ‘\( Gs/ + \) females superficially resemble \( Ta/ + \) females. \( Gs/Y \) males and \( Gs/Gs \) females have uniformly shiny fur. They lack the following features of \( Ta/Y \): sticky [i.e. hairless] tail, bare patches behind ears, decrease in yellow pigment along mid-dorsal.’

**STRIATED**

This gene was probably induced by X-rays (Phillips, 1963). \( Str/ + \ \varnothing\) superficially resemble \( Ta/ + \ \varnothing \) in having dark transverse stripes; however, the stripes are often not distinguishable clearly until the animals are 16–18 days old, and there is some normal overlapping. \( Str \ \varnothing\) are not viable (death between 11\( \frac{1}{2} \) and 13 days of gestation). Striated is about 8 units from \( Ta \) (Lyon, 1966b) and has a different pathology (Lyon, 1963): the black stripes are due to a local shortening of hairs which exposes the dark base of the hairs behind; there is no absence of (segmented) zigzags as in \( Ta \). \( Str \) thus affects hair structure rather than pigmentation. According to Lyon, smaller patches of short hair are sometimes not visible unless the fur is brushed back, and the regular transverse stripes are only part of the story.

As the (potential) phenotype of \( Str \ \varnothing\) is unknown, that of \( Str/ + \ \varnothing\) cannot give critical evidence in favour of the L.H. However, as will be shown presently, it can quite critically rule it out. As seen in dry preparations at medium microscopic magnifications, all the hairs from short patches are grossly abnormal. The hairs as a whole appear irregularly wavy somewhat like the ‘de-kinked’ hairs of some Negro women. The hair calibre varies considerably along the length of the hair and, as a consequence, repeated short sections of septate and septulate structure may follow each other. Many hairs, and particularly the zigzags, are flat ribbons which tend to be axially twisted. Details will be reported on a later occasion. Now, according to the L.H., the long hairs of these mice should be normal. This, however, is far from the truth. In virtually every hair, slight irregularities of septation and minor changes of calibre are clearly detectable which do not occur in the normal coat, and it is difficult, if indeed possible, to find a hair which is normal throughout its length. Clearly, the action of the \( Str \) gene is not confined to the short patches, but affects the coat as a whole, and the difference between short patches and the remainder of the coat is one of degree and not of kind. This is only possible if both alleles are active throughout the coat of \( Str/ + \ \varnothing\), and this, for the gene in question, critically rules out the mechanism postulated by the L.H.

**MOTTLED, BRINLED, DAPPLED AND TORTOISESHELL**

The heterozygotes for all these genes (Falconer, 1953; Fraser, Sobey & Spicer, 1953; Dickie, 1954; Lyon, 1960; Phillips, 1961) show a similar type of mottled fur. As the hemizygotes perish before birth or, in the case of brindled (\( Mo^{br} \)), in the nest, direct tests for allelism cannot generally be carried out; how-
ever, by the use of an exceptional $Mo^{br}$♂ which survived and was fertile (a ‘Durchbrenner’, to use Hadorn’s expression), the allelism of $Mo^{br}$ and dappled ($Mo^{dp}$) has been virtually proved: the putative $Mo^{br}/Mo^{dp}$ ♀♀ had the near-white phenotype of $Mo^{br}$♀♂ and died at about the same age. Allelism is, in any case, likely on account of the similarity of phenotype of the heterozygotes and similar linkage relations with $Ta$ which is about 4 units away (though the latter is not yet known for tortoiseshell).

The original description of mottled ($Mo$) by Fraser et al. (1953) speaks of ‘many regions of light-coloured (off-white) hair scattered without pattern over the body’ and adds that ‘Mottled and Brindled females are similar both in the colour of the off-white regions, and in random scattering of them over the body’. This may be accepted as a first approximation. However, Falconer (1953) observed that the diffuse areas of very lightly pigmented hairs are ‘sometimes arranged in an irregular pattern of transverse bars reminiscent of the markings of Tabby heterozygotes’, an observation which I can confirm. It thus seems that the markings of $Mo/+$ and $Mo^{br}/+$ ♀♀ are not strictly random though the transverse pattern is less obvious and regular than that of $Ta/+$ and $Str/+$ ♀♀.

All four heterozygotes show some waving or curling of the whiskers, and for tortoiseshell, at any rate, a silkier hair texture has also been reported (Dickie, 1954). The vibrissae of $Mo^{br}$♀♂ are strikingly curly, and the hairs of the coat are also affected (Falconer, 1953). Recent observations by the present author show that the fur consists of the usual hair types, but the structure of the hairs is grossly abnormal. Details (also on $Str$ and other genes affecting hair structure in the mouse) will be published in due course. As seen in dry preparations, the transverse structure of the hairs is interrupted irregularly over shorter or longer distances, perhaps due to absence of septa, more probably due to the presence of liquid in the hair. Often there are fluctuations in hair calibre not found in normal hairs and various other abnormalities. The picture as a whole is striking and recognizable at a glance. As one might expect, a similar but less extreme situation is encountered in the light-coloured patches of $Mo^{br}/+$ ♀♀ which, incidentally, include many hairs which are partly pigmented. However, structural abnormalities are by no means confined to the light-coloured areas. Almost without exception, pigmented hairs have milder but easily detectable irregularities in septation and often fluctuations in hair calibre. It is obvious that the whole of the fur of $Mo^{br}/+$ ♀♀ is involved, and not only the light-coloured patches. Where the structural abnormalities are slight, pigment is formed; where they are severe, pigment is reduced or absent. Evidently, $Mo^{br}$ (and presumably the other mottled alleles) affects hair structure in the first instance, and pigmentation is only secondarily involved where the structural anomalies are severe. Beyond any doubt, the light-coloured areas are due to a threshold mechanism, and in the fur as a whole, both alleles are active as in an ordinary autosomal heterozygote.
Tabby mouse and Lyon hypothesis

This is in agreement with the findings of Phillips (1961) in the dappled \( (Mo^{dp}/+) \) heterozygote where the amount of curling of the whiskers is correlated with the degree of lightness of the coat at weaning: "the greater the curling, the lighter the coat", i.e. the more severe the structural abnormalities, the fewer hairs are able to form pigment. On the other hand, Phillips (1961) did not succeed in selection experiments for lighter and darker strains; this negative finding, of course, does not discriminate between the hypotheses.

We mention here briefly a similar sex-linked gene, blotchy (Russell, 1960; Russell & Saylors, 1962; Lyon, 1966), also about 4 units from \( Ta \) and possibly (probably) an allele of mottled. 'Heterozygous females have irregular patches of more diluted fur. Expression is occasionally poor at weaning age... but is complete at adulthood. Hemizygous males, hemizygous females (XO), and homozygous females are light all over (no blotching)... Their whiskers are kinked at birth but straight by the time of weaning...'

The fact that, like \( Ta \) and \( Str \), the mottled alleles affect hair structure in the first instance will prove of importance in the interpretation of experiments (Lyon, 1963) to be discussed on a subsequent occasion. In that paper, Lyon treated the mottled series as colour genes like albinism (\( c \)) or pink-eyed dilution (\( p \)). In the light of the facts presented in this paper, this obviously requires modification and reassessment of the situation.

Bent-tail and other sex-linked genes in the mouse

The semi-dominant gene for bent-tail \((Bn; Garber, 1952)\) has been claimed to provide supporting evidence for the L.H. (Lyon, 1966a). The only published data on its anatomy and development are my own (Grüneberg, 1955). Whereas penetrance is complete in \( Bn \delta \), there are some normal overlaps in \( Bn / + \varphi \). Normal overlapping is found in countless autosomal genes and thus cannot be used to discriminate in favour of one hypothesis rather than the other. In \( Bn \delta \), the anomalies start with the 6th caudal vertebra and steadily increase in frequency to a plateau which is maintained in the distal parts of the tail. In \( Bn / + \varphi \), the general pattern is the same, but expressivity is lower. In 14 \( Bn \delta \), there was an average of 5.07 severely affected vertebrae (with double centres) and of 8.07 mildly affected vertebrae per mouse. If the vertebral anomalies in \( Bn / + \varphi \) were due to inactivation of the normal allele in the sense of Lyon, they should show a similar ratio. In actual fact, 27 manifesting \( Bn / + \varphi \) had an average of 0.70 severely and 6.96 mildly affected tail vertebrae. Evidently, in the manifesting region, both alleles are active to bring about this lowered expressivity. The evidence provided by the \( Bn \) gene is thus against the L.H.

Several of the remaining sex-linked genes in the mouse have not yet been described in any detail, and none of them provides any critical information for or against the L.H. Jimpy (Phillips, 1954) is a sex-linked recessive gene which in \( \alpha \alpha \) causes intention tremor and later convulsions, with death round about
28 days. A single manifesting jimpy female (which was $Ta +/+ jp$ and hence not an $XO \varphi$) has been explained as probably due to somatic crossing over, a sector including part of the CNS becoming homozygous $jp/jp$ (Grüneberg, 1966a). Gyro, according to preliminary reports by Lyon (1960, 1961), in $\varphi\varphi$ shows circling behaviour with deafness, abnormalities of the long bones and ribs and sterility; heterozygous $\varphi\varphi$ show incomplete penetrance of the circling behaviour and apparently no skeletal abnormalities. Scruvy (Russell, Russell & Gower, 1959), sparse fur (Russell, 1960a), and sex-linked anaemia (Grewal, 1962) are all recessive without any known manifestations in heterozygous $\varphi\varphi$. The same applies to a sex-linked lethal (Hauschka, Goodwin & Brown, 1951), if the existence of such a gene was the correct interpretation of the anomalous segregations observed by these authors. Finally, there is a sex-linked histocompatibility gene (Bailey, 1962) so far only reported in an abstract which contains no relevant information.

**MOTTLED-WHITE IN THE GOLDEN HAMSTER**

This condition (Magalhaes, 1954) is lethal in $\varphi\varphi$ whose potential phenotype is thus conjectural. Heterozygous $\varphi\varphi$ 'have a thinner than normal coat with normal colored fur intermingled with white. Some animals are almost entirely white while others are only slightly grayer than normal.' Hair structure as well as colour is thus involved as in the mottled alleles in the mouse, and pending a microscopic study of both white and pigmented regions of the fur, the 'mosaic' nature of these heterozygotes is clearly problematical.

**STREAKED HAIRLESSNESS IN CATTLE**

This sex-linked condition in Holstein-Friesian cattle (Eldridge & Atkeson, 1953) has been claimed in support of the L.H. (Lyon, 1966a). As affected $\varphi\varphi$ are not viable, their (potential) phenotype is unknown. Supposing they were, in fact, completely hairless, heterozygous $\varphi\varphi$ should, on an average, be half-hairless. This is very far from the truth, as 'It was roughly estimated that not more than 5% of the hide was lacking in hair in the most severely affected animal'. Moreover, the arrangement of the hairless areas is not random. 'The affected cattle were found to have areas devoid of hair on various parts of the body, the hairless areas occurring in more or less consistent patterns. On all affected animals there were approximately perpendicular hairless streaks over the thurls, some more extensive than others, with considerable variation between the two sides of the same animal...' Clearly, this case does not support the L.H.

**THE TORTOISESHELL CAT**

Unlike the sex-linked genes in mouse and hamster which affect hair structure (with or without involvement of pigmentation), in the tortoiseshell cat pigmentation (eumelanin versus phaeomelanin) seems to be affected in the first instance.
These two pigments generally occupy separate sites such as in the banded agouti hairs, or on the ventral surface of $d'$ mice, etc. Several species of animals have series of multiple alleles which go from one extreme to the other. Thus all fur pigment in the lethal yellow mouse ($A^v$) is phaeomelanin and all fur pigment in extreme non-agouti ($a^e$) is eumelanin. Some alleles seem to be teetering on the brink; in viable yellow ($A^v v$; Dickie, 1962), whereas the baby coat is usually a clear yellow, many animals subsequently become irregularly mottled with black patches intermixed with yellow (and sometimes with agouti hairs), a pattern very much like that of the tortoiseshell cat. A similar situation occurs in the Japanese rabbit ($e^i$), a member of the extension series which also spans the whole range from eumelanin to phaeomelanin, and in the tortoiseshell ($e^p$) guinea-pig. In the latter animal, a remarkable case of factor interaction has been known for a long time; it is described by Sewall Wright (1963) as follows:

'Tortoise shells of genotype $S S e^p e^p$ are predominantly eumelanic but usually show scattered yellow hairs and less frequently more or less yellow in blotches. With $s s e^p e^p$ or even $S s e^p e^p$, the amount of yellow is increased and there is a strong tendency to segregation of yellow and eumelanin into a few large areas each often with scattering admixture of the other color. These areas are often separated in whole or in part by white streaks. Sometimes a streak between eumelanic areas is white at one end, yellow at the other, indicating that the determination of yellow is related to the process that leads in more extreme cases to white by absence of the pigment cells.'

As every observer of cats knows, the same interaction is strikingly present in the tortoiseshell cat. To quote an early source (Whiting, 1919), "\"Self\" tortoise-shells have yellow hair closely intermixed with non-yellow... Tortoiseshells with restricted white-spotting tend to have yellow separated into patches, while further extension of white separates yellow and non-yellow areas still more. Separation of yellow into patches appears not to be correlated with amount of yellow.\"

$A^v v$ in the mouse, $e^i$ in the rabbit and $e^p$ in the guinea-pig are all autosomal genes, and it is obvious that in all of them, the eumelanin-phaeomelanin dichotomy is the result of a threshold mechanism and not the result of chromosome inactivation. The physiological process in the tortoiseshell cat is obviously the same, notwithstanding the fact that it happens in a heterozygote rather than in homozygotes as in the other animals. To invoke a threshold for the autosomals and chromosome inactivation for the sex-linked gene would be an arbitrary procedure which could not strengthen the L.H. Similarly, in the guinea-pig, the influence of spotting genes on the manifestation of $e^p$ is clearly a case of factor interaction, and there is no justification for a totally different interpretation in the analogous case in the cat. Indeed, as has been pointed out above, according to the L.H. chromosome inactivation must be refractory to the effects of other genes, and the tortoiseshell phenotype plainly is not. So far from supporting the L.H., the tortoiseshell cat increases its difficulties.
DISCUSSION

Of all the sex-linked genes in the mouse, tabby affords the best opportunities for a critical test of the L.H. Six different test criteria are applicable, and in every single instance the evidence goes clearly against the L.H.

1. There is a clear-cut pattern (fur, vibrissae, molars).
2. Contrasted areas differ from the hemizygous phenotypes (fur).
3. Intermediate areas are regularly present (tail rings).
4. Contrasted areas are unequal in the aggregate (fur, molars).
5. The heterozygous phenotype responds to selection (vibrissae, stripes).
6. Resemblance of heterozygous manifestation to that of autosomal mimic (molars).

With everything against and nothing in favour of the hypothesis, attempts to explain away by *ad hoc* assumptions one or the other of these items (perhaps no. 2) will not carry conviction: the rest of the evidence, so far as I can see, cannot be shaken without abandoning essential parts of the hypothesis in the process. In conformity with previous findings in the molars (Grüneberg, 1966b), we must conclude that the known phenotype of $Ta^+\,\varnothing\varnothing$ cannot be explained in terms of the Lyon hypothesis. Its whole behaviour is in agreement with the conclusion that both alleles act together in the same way as in heterozygotes for autosomal genes.

Decisive evidence against the L.H. also comes from the mottled series and from striated. Disregarding lesser points, the structural abnormalities of the coat are not confined to the unpigmented or short-haired areas respectively, but occur in a milder form throughout the pelage. The fur of the heterozygotes is thus clearly not a patchwork of normal and mutant areas: both alleles act together over the whole area of the coat, with some regions more severely affected than others and hence unpigmented or short-haired, respectively. In $Bn^+\,\varnothing\varnothing$ the pattern of tail abnormalities is similar to that in $Bn\,\varnothing\varnothing$, but its lower expressivity shows that both normal and mutant allele are active. In the latter case, *ad hoc* assumptions (non-autonomous development, etc.) would remove the gene from the category of contradicts to that of non-discriminators, but no more.

The mottled-white gene in the golden hamster is very similar to the mottled series in the mouse and may well be homologous to it. In the absence of evidence to the contrary, there is no reason to suppose that its heterozygous phenotype is a patchwork mosaic in the sense of the L.H. any more than that of $Mo^{br}^+\,\varnothing\varnothing$ in the mouse. The heterozygous phenotype of streaked hairlessness in cattle disagrees with the consequences of the L.H. in every respect, quite apart from the fact that the phenotype of the hemizygote is unknown. The eumelanin–phaeomelanin dichotomy of the tortoiseshell cat has autosomal counterparts in mouse, rabbit and guinea-pig, and in the tortoiseshell cat and in the tortoiseshell guinea-pig there is also the same interaction with spotting genes which separate
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the two kinds of pigment into distinct areas. Clearly, none of these genes in hamster, cattle and cat gives any support to the L.H., and the tortoiseshell cat, at any rate, raises considerable difficulties for the hypothesis.

Taken one at a time, and in a structurally normal X-chromosome, none of the sex-linked genes in the mouse thus agrees with the L.H. Returning to the starting point of the hypothesis, the peculiar heterozygotes for Ta, Str and Mo turn out to be the result of threshold mechanisms like countless others in the autosomes, and not to be explicable by 'phenotypic segregation' of chromosomes which is another way of expressing the L.H. Evidently, in mouse females, there is no inactivation of whole X-chromosomes, and the data discussed in this paper do not suggest that there is any inactivation at all. This, of course, does not rule out the possibility that instances of inactivation of individual sex-linked genes may yet be discovered, but this is a concept totally different from the L.H.

Henceforth, as a minimum requirement, claims that the phenotype of a heterozygote conforms to the L.H. will have to be based on the criteria discussed in this paper: mere assertions will not do.

The question arises of whether the behaviour of the sex-linked genes in the mouse calls for any special explanation. The present author feels that it would be rash to answer this question in the negative. It may be peculiar that there are six semi-dominant genes (Ta, Str, Mo, Gs, Bn, Gy) and only four recessives (jimpy, scurfy, sparse fur and anaemia), disregarding the histocompatibility gene and the lethal which belong to a different category. It is difficult to obtain an estimate of the ratio of 'dominant' to 'recessive' autosomal genes in the mouse, if only because these are not distinct categories, and small effects in the heterozygote can probably be discovered in the majority of cases commonly referred to as recessives. However, if we omit histocompatibility genes, 'biochemical' mutants and the like, and if we count as semi-dominant any locus which has given rise to at least one such allele, it seems that autosomal 'recessives' exceed genes with easily detectable effects in the heterozygote by roughly 3:1. Hence the X-chromosome of the mouse (disregarding the possibility of a bias in their discovery) probably has more than its fair share of such genes. Amongst these, the group of hair structure genes (Ta, Str, Mo and probably Gs) stands out. The question therefore arises of how common are autosomal genes of this kind, and do they include instances where the heterozygote is poised as closely to the threshold of manifestation as in the sex-linked trio (or quartet) of genes. Excluding colour and spotting genes, the *Mouse News Letter* no. 34 (1966) lists some 30 loci which clearly affect skin and/or pelage of the mouse; many of them have not yet been published, and some may ultimately turn out to be allelic to each other. They include about nine semi-dominants or dominants, none of them with a variegated or striped heterozygous phenotype comparable to the sex-linked ones. On this basis it would appear that the sex-linked genes do in fact differ from the autosomal genes affecting hair structure.

However, the case of the mottled series may not be unique, and there may be
more structure genes masquerading as colour genes, etc. The study of hair structure in the mouse is a badly neglected field. Even grossly abnormal coats have in many instances never been investigated, and nobody, apparently, has thought of examining the coat of 'colour mutants' for the possible existence of structural anomalies of the fur. Following the study of the coats of the sex-linked genes, the present author has started to make a survey of various autosomal conditions not hitherto suspected of affecting hair structure. The result has been quite surprising, and the full exploitation of the large field opened up will take time. Here, two examples may suffice. The clumping of eumelanin pigment in dilute \((d/d)\) has been known for a long time, and it is perhaps not surprising that clumping of phaeomelanin in these animals has now also been found; but indeed the hair structure of these animals is characteristically abnormal, and the suspicion arises that this may be more basic than the colour effect by which the gene has been discovered in the first instance. The second example concerns the grey-lethal gene which I described more than 30 years ago: absence of yellow pigment seemed obvious from inspection of the coat which was pure grey and lacked the yellow colour in the agouti bands. Microscopic examination now shows that phaeomelanin is, in fact, present in the form of a few massive clumps (much like the eumelanin clumps in dilute mice); but the hairs themselves are structurally abnormal, and this may well be behind the clumping of the yellow pigment. In grey-lethal and brindled alike, the assessment of the mutants by visual inspection has misled the respective authors!

The most striking case of autosomal mottling is the varitint-waddler mouse (Cloudman & Bunker, 1945); \(Va/+\) mice show irregular and finely interspersed areas of white, dilute and normally pigmented hairs; the dilute areas gradually tend to become white with increasing age. Like the mottled genes which it resembles phenotypically, varitint-waddler is now also unmasked as a gene affecting both hair structure and melanin formation. The white hairs are grossly abnormal in structure, the grey ones rather less so, whereas the normally pigmented hairs are structurally nearly, but apparently not quite, normal. Evidently defective pigmentation is secondary to abnormal hair structure, and the colour changes with age reflect a gradual deterioration of hair structure.

Some of the ordinary autosomal spotting genes are remarkably similar to the sex-linked mottled series. Thus, the homozygotes of dominant spotting \((W/W', W^o/W^o', \text{etc.})\) are uniformly white, the respective heterozygotes, on certain genetic backgrounds, variegated (and \(W^o'/+\) also dilute). Similarly, the homozygotes for microphthalmia and for white \((mi/mi \text{ and } M^{1wh}/M^{1wh})\) are white, the \(+/mi \text{ and } M^{1wh}/+\) heterozygotes, on certain genetic backgrounds, spotted (though not variegated; the latter also with some dilution of fur colour). Other spotting genes have more regular and more sharply defined patterns of black and white, and the respective homozygotes are usually not completely white. An increasing body of information shows that in several of these genes spotting is not merely a matter of pigmentation, but also involves hair structure, and this
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may well turn out to be true for most if not all of them. As critical and quantitative studies will take time, we shall here confine ourselves to pointing out the essential similarity of autosomal and sex-linked genes whether their phenotype is compared by inspection or by microscopic examination.

Manifestly, sex-linked and autosomal heterozygotes in the mouse do not differ in kind. In both groups, cases occur in which the physiological interaction between the two alleles brings about a situation in which a developmental threshold is crossed in some parts of the body, but not in others. The suspicion remains, however, that this kind of situation may be commoner in sex-linked than in autosomal heterozygotes, and that something in the X-chromosome may tend to keep alleles in a state of semi-dominance rather than to allow one allele to gain complete ascendency over the other. This is also suggested by the behaviour of genes in structural heterozygotes, with which I hope to deal on a later occasion.

The relationship between hair structure and pigmentation discussed above is not peculiar to the mouse. Mudge (1908) described a transitory ghost pattern in albino rats (*Rattus norvegicus*) homozygous for the hooded gene, and Goldschmidt (1927) mentioned a tiger embryo in which the future transverse stripes were clearly visible long before pigment formation in the shape of thickenings of the skin. Many people will also be familiar with the ghost tabby pattern in certain black cats, and with the ghost rosettes in black panthers.

[Note added September 16, 1966, Since this paper was written, a scrutiny of the sex-linked genes in man indicates that they provide as little evidence in favour of the Lyon hypothesis as their counterparts in the mouse and other mammals. The evidence will be published shortly (‘Sex-linked genes in man and the Lyon hypothesis’, *Ann. Hum. Genet.*, in the press).]

SUMMARY

The Lyon hypothesis (L.H.) of dosage compensation of sex-linked genes in mammals postulates that in the female, during embryonic development and at the cellular level, either the paternal or the maternal X-chromosome is inactivated; that this inactivation happens at random; and that it persists in the descendants of the cell in which it has taken place. The genetic evidence hitherto adduced as favouring the L.H. has mainly involved complex situations such as the simultaneous segregation of two sex-linked genes and/or the behaviour of genes in structurally abnormal chromosomes.

By contrast, this paper examines the behaviour of sex-linked genes in mammals (other than man) taken one at a time and in structurally normal X-chromosomes. Criteria are discussed by means of which the validity of the L.H. in such genetically simple situations can be tested. These tests reveal that the behaviour of heterozygotes for three sex-linked genes in the mouse (tabby, striated, brindled) is decisively at variance with the L.H., and the same is probably true for a fourth gene, bent-tail. The remaining sex-linked genes in the mouse give no evidence for or against the L.H. As there is thus clear evidence
that in three, and probably in all four instances, both alleles are active as in ordinary autosomal heterozygotes, it is evident that in the mouse there is no inactivation of a whole X-chromosome. Indeed, the facts discussed in this paper (including those of one instance each in hamster, cattle and cat) do not suggest that there is any inactivation at all.

Nonetheless there is a suspicion that heterozygotes for sex-linked genes, taken as a group, may include more cases of semi-dominance than occur in autosomal heterozygotes. If this should be substantiated, it would require an explanation.

**ZUSAMMENFASSUNG**

*Weitere Mitteilungen über die tabby Maus und die Lyon-Hypothese*


Andererseits besteht ein Verdacht, dass Heterozygoten für geschlechtsgebundene Gene öfter als solche für autosomale Gene sich intermediär verhalten. Sollte sich dies bestätigen, würde eine besondere Erklärung erforderlich sein.

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