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The case for somatic crossing over in the mouse

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1. INTRODUCTION

As mutations make a silent entry into this world, many of them are not noticed until long after they have arisen. However, the history of origin of dominants with regular manifestation and that of sex-linked genes is often well authenticated. As most of these reports show nothing out of the ordinary, little notice has been taken of a minority of mutations which have happened under rather odd circumstances. This is partly due to the fact that the mutant genes in question have subsequently behaved in a perfectly normal manner, and that individual instances are usually open to various interpretations between which a decision cannot be made after the event. However, though individual strange cases may do little but cause a momentary raising of eyebrows, a rather consistent pattern is beginning to emerge now that a series of such instances is available for scrutiny. The present paper is an attempt to look for a common denominator for various oddities which have been reported in mosaics and in freshly arisen mutations in the mouse, and occasional peculiar situations observed later on. Somatic crossing over as a possible explanation of a mosaic in the mouse was first discussed by Carter (1952). But whereas at that time the supporting evidence was still somewhat meagre, the material brought together here leaves little doubt that somatic crossing over does, in fact, occur in the mouse and other laboratory rodents, and presumably in all mammals.

In extracting the material from the literature, completeness has not been aimed at, but it is believed that the majority of the strange cases has been included in the survey and that in any case the sample may be regarded as representative. Only cases published in scientific journals have been included, but no attempt has been made to extract similar information from the *Mouse News Letter*.

2. MOSAICS IN HETEROZYGOTES

In rare instances, an animal heterozygous for a recessive gene (generally affecting the coat) shows a patch of fur with the recessive phenotype. Though somatic mutation from the wild-type to the mutant allele is one of the possible interpretations, this type of mosaicism, in the mouse as well as in other laboratory rodents, is more readily explicable by somatic crossing over and will therefore be discussed in this paper.

In the mouse, three cases of $+/b$ heterozygotes with a brown patch each (2♂♂,

1♀) and all piebalds (*s*/*s*) have been described by Pincus (1929 *a*), and a similar case (in a piebald ♀) by Fisher (1931). Feldman (1935) reported two mosaics involving the gene for pink-eyed dilution which arose in piebald +/*p* mice (1♂, 1♀) born in two successive litters of the same parents; one of them included the eyes which were pink. Carter (1952) described a female mosaic heterozygous for the viable allele of dominant spotting (W^v/+); she had two large patches with full pigmentation which presumably lacked W^v; on the other hand, she transmitted a significant excess of W^v gametes to her offspring (31 W^v; 10+). Several mosaics were reported by Morgan & Holman (1955); these include one belted (*bt*/*bt*) ♀ which may have been +/*b* like Pincus's and Fisher's mice; one piebald and two belted ♀♀ where the mosaic may have involved a change at the albino (*c*) or dilution (*d*) locus, and one similar instance of two piebald litter mates (1♂, 1♀); finally, there was one yellow-black mosaic ♂ (A^y/*a*). Mosaics induced by X-irradiation of 10¼-day-embryos of the constitution + +/*p* c^{ch}; +/*b*; +/*d* have been described by Russell & Major (1957); as judged by the phenotype, at least three and probably all four of the genes were expressed in one or the other of the spots.

In the rat (*Rattus norvegicus*), Castle (1922) described a hooded ♂ of the constitution *p* +/+ *c* which, in the pigmented parts of its coat, had numerous scattered spots which varied in size from a few yellow hairs to a large area about an inch square which corresponded in colour to the genotype *p*/*p*. The animal did not transmit the mosaic condition to any of its very numerous offspring. A blue-black mosaic in a hooded ♀ has been reported by Curtis & Dunning (1940); it occurred in the F_2 generation of a cross between intense hooded and blue self rats; the pigmented area covered about 26% of its coat; about 10% was black and 16% blue; crossed to a blue (*d*/*d*) ♂, she produced sixteen young, all blue.

In the rabbit, Castle (1929) described a +/*d* Dutch ♂ with a large blue patch; three of his 100 black Dutch offspring again had a blue patch; one of these, a son, sired three tricolour young out of eighty-three; there were thus seven black-blue mosaics in this descent of rabbits. A solitary case of a +/*d* Dutch ♂ with a blue patch is due to Pickard (1936). The same author (1929, 1936) reported a rabbit ♂ which was heterozygous for both brown and angora fur (+/*b*; +/*l*); this animal had four fur areas which were brown and three with long angora hair; the mosaic patches did not overlap.

Finally, in the guinea pig, three mosaics, all of them piebalds, were reported by Wright & Eaton (1926); two of them (1♂, 1♀) started life with the constitution +/*f*, the third, a ♀, was +/*p*.

As a starting point, let us assume that all the mosaics in rodents which began life as heterozygotes form a homogeneous group as regards the underlying mechanism. This assumption is tenable if one, at least, of the six (or more) possible mechanisms can account for all of them. Naturally, it is not necessarily the one actually at work. Nor, despite the parsimony principle, should one take the homogeneity of the group for granted if such a mechanism is demonstrably or probably true for only a small minority of the cases; the extrapolation to the majority may not be legitimate.

(1) *Somatic mutation.* This implies that in a heterozygote $+/x$, the normal allele + during development has mutated to the recessive x to give an x/x patch. Unless special 'mutator' conditions are invoked, somatic mutation will not account for multiple cases (e.g., two mosaics for p in successive litters (Feldman, 1935); two similar mosaics in the same litter (Morgan & Holman, 1955); seven d mosaics in a descent of Dutch rabbits (Castle, 1929)). Similarly, Pickard's (1929, 1936)brown-angora mosaic would require two simultaneous mutations in different genes. Carter's (1952) $W^v/+$ mosaic with $+/+$ patches in the fur and apparently W^v/W^v tissue in part of the gonad would require two mutations in opposite directions at the same locus. We conclude that somatic mutation cannot be the common cause of these mosaics, and may not be the cause of any of them.

(2) *Chromosome elimination or deletion* gives rise to a patch of $0/x$ tissue. Again, this is difficult to maintain for multiple cases without invoking special genetic conditions which favour these events. The hypothesis is incompatible with Carter's (1952) case; elimination of a whole chromosome will also not account for a phenotypically p patch induced by X-rays in a mouse of the constitution $+ +/p\ c^{ch}$ (Russell & Major, 1957).

(3) *Somatic reduction* would lead to the formation of twin spots $+/0$ and $0/x$ respectively. It is found sporadically in higher plants (Huskins, 1948) and has been reported as occurring during metamorphosis in the hind gut of the mosquito *Culex pipiens* (Grell, 1946); in the latter case, cells which have become highly polyploid as the result of endomitosis are brought back to an octoploid or tetraploid state. In his analysis of somatic crossing over in *Drosophila*, Stern (1936) found no evidence for somatic reduction, nor did Fankhauser & Humphrey (1954) in the axolotl. Two, at least, of the mosaics described above cannot be explained in terms of somatic reduction. In Castle's (1922) $p\ +/+\ c$ rat, somatic reduction would have produced two kinds of spots, p and c respectively whereas p spots only were found; and in Russell & Major's (1957) $+ +/p\ c^{ch}$ mouse, somatic reduction would have uncovered both genes rather than p alone.

(4) *Somatic non-disjunction.* This possibility was discussed by Carter (1952) in connection with his $W^v/+$ mosaic. If so, the whole or part of the gonad would be $W^v/W^v/+$ and the fully coloured patches +. As pointed out by Carter, this mechanism cannot account for Pickard's (1929, 1936) brown-angora mosaic; if the two genes are not linked, two separate events are required; if they are linked and in coupling, the brown and angora patches should have coincided; and if in repulsion, there should have been either patches of angora or of brown but not both, since a rabbit of the constitution $b\ +/+\ l$ could show non-disjunction either of type $b\ +/b\ +/+\ l$ and $+\ l$ or of type $b\ +$ and $b\ +/+\ l/+\ l$.

(5) *Physiological inactivation of the dominant allele.* In this case the mosaic spot does not differ genetically from the rest of the animal which may be symbolized thus $(+)/x$. Pincus (1929*a*) made this suggestion to account for the fact that mosaic spots tend to occur in localities which, in spotted animals, are white; perhaps in such critical areas the dominance of the + allele is occasionally weakened. As the localization of the mosaic spots is by no means always as in Pincus's

mice (see, for instance, Castle's (1922) rat), the original argument loses some of its force. Moreover, Pincus's hypothesis implies the existence of unpigmented melanocytes in the white areas of piebalds which can be reactivated locally (in which case they might form the pigment characteristic of the recessive allele). But it is now known that the white areas of spotted animals lack melanocytes altogether (Billingham & Silvers, 1960). The inactivation hypothesis cannot account for Carter's (1952) $W^v/+$ mouse as the anomalous segregation ratio is clearly genotypic in origin. We have mentioned the inactivation hypothesis here mainly for the reason that a variant of it has recently been invoked by Lyon (1961) to account for mosaicism of sex-linked recessives, such as orange versus black in the tortoise-shell cat. We shall have to come back to that concept in a later section dealing with mutations in the X-chromosome.

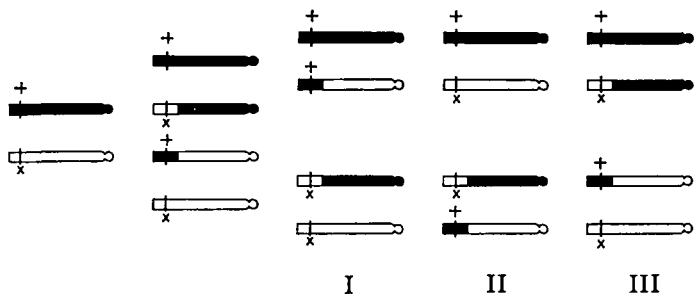

Fig. 1. Diagrammatic representation of somatic single crossing over based on the work of Stern (1936).

(6) *Somatic crossing over.* Somatic crossing over in *Drosophila* was analysed in much detail by Stern (1936). Somatic, like meiotic, crossing over takes place in the four-strand stage, and the subsequent separation of the centromeres is equational (I and II in Fig. 1); there is no evidence that reductional separation of centromeres (III) ever occurs. Considering single crossing over only, separation of centromeres according to modus I leads to homozygosity for genes distal to the level of exchange for which the animal was originally heterozygous; separation according to modus II leaves the original heterozygosity unchanged. In the case of a recessive gene, only the twin patch x/x will be detectable phenotypically (provided, of course, that it is in the right part of the body and that the development of the gene in question is autonomous).

In the mouse, somatic crossing over was first suggested by Carter (1952) to account for his $W^v/+$ mosaic. The fully coloured areas would be $+/+$, and part of the gonad (say, one ovary) would be W^v/W^v. The concept can account for all the cases discussed in this section, and in some of them better than the other mechanisms considered. In particular, the multiple cases (similar mosaics in the same litter, in successive litters, or in a descent) present no difficulties. In *Drosophila*, the incidence of somatic crossing over is greatly increased in flies carrying various Minute (*M*) 'genes' (Stern, 1936), and it seems reasonable to assume that similar

enhancers of somatic crossing over also exist in mammals. It has been pointed out by various authors that most of the mosaics have occurred in spotted animals. (Exceptions are Pickard's brown-angora rabbit which only had white fore feet and a white nose tip, and Morgan & Holman's A^y/a mosaic which was self.) Perhaps the spotting genes in mammals enhance the frequency of somatic crossing over as do the Minutes in *Drosophila*.

Castle's (1922) p mosaic in the rat can be accounted for by a single crossover between p and c if the order is

$$p\text{—}c\text{—centromere}$$

or by a double crossover if c should be distal in relation to p. The same applies to the phenotypically p spot induced by X-rays in a $+\ +/p\ c^{ch}$ mouse by Russell & Major (1957).

Pickard's (1929, 1936) brown-angora mosaic would require two separate crossover events if the two genes segregate independently of each other. In the presence of a gene enhancing somatic crossing over this might well happen. If they should be linked and are in repulsion ($b\ +/+\ l$), a crossover between the centromere and the more proximal of the two would lead to daughter cells with the constitutions $b\ +/b\ +$ and $+\ l/+\ l$ respectively. The two genes are not closely linked, but loose linkage is not excluded by the data available (Robinson, 1956).

Finally we come to Curtis & Dunning's (1940) blue-black mosaic rat (also, like the preceding case, already discussed by Carter). It came from a mating $+/d \times +/d$ and bred as d/d; the authors suggested that the animal started with that constitution, and that the intense (black) mosaic area was due to a somatic reverse mutation from d to $+$. It is equally possible that the animal started as $+/d$ and that somatic crossing over led to the formation of $+/+$ (the black mosaic spot) and d/d areas, the latter including the rest of the pigmented fur and the gonads. As the mosaic rat came from two $+/d$ parents, it is more probable that the $+$ gene was a heritage from its parents than that it arose afresh by reverse mutation.

To sum up. Somatic crossing over alone, of all the mechanisms considered, can satisfactorily account for all the mosaics which arose in heterozygotes (or probable heterozygotes). It may, in fact, be the mechanism underlying all these cases. Additional evidence for the occurrence of somatic crossing over in the mouse will be presented in the next section.

3. ADDITIONAL EVIDENCE FOR SOMATIC CROSSING OVER IN THE MOUSE

This is the place to discuss two unusual events for which no satisfactory explanation has hitherto been available.

In 1936, Castle, Gates, Reed & Snell reported on a linkage experiment involving the genes dilute (d) and short-ear (se) in the mouse which are very closely linked (about one crossover in 800 gametes). Castle *et al.* observed two of these rare crossovers, both of them ♂♂, in a single litter. As this is an improbable event on a chance basis, the authors suggested that these two animals were a pair of identical

twins. Now, as pointed out by Stevens (1937), the coincidence of a rare crossover with identical twinning is also an improbable event, unless identical twins are very common in the mouse; and in his own data, Stevens found no evidence at all for the occurrence of twins. The difficulty disappears if it is assumed that crossing over which occurred in the + +/*d se* mother of these two ♂♂ was a somatic and not a meiotic event; i.e., that one of her ovaries included such a sector.

The other peculiar story involves the genes for Caracul (*Ca*) and belted (*bt*) in linkage group 6 (map distance about 12 units). In the first litter of a mating *Ca* +/+ *bt* ♀ × + *bt*/+ *bt* ♂, MacNeil (1957) obtained two ♂♂ which bred as *Ca*/*Ca* homozygotes. One of them bred as *Ca* +/*Ca bt*. The other, on being mated to a *bt*/*bt* sister, produced twenty self and two belted offspring. Assuming that the male in question was heterozygous for *bt*, this is a very poor fit to a 1:1 ratio ($P = 0{\cdot}0001$ approx.). Actually, one, at least, of the two belted young had a poorly developed belt and may have been +/*bt* (his *bt* gene being derived from the *bt*/*bt* mother); no record was made of the belt of the other young, but heterozygous manifestation of *bt* is sufficiently common to make it plausible that the second belted young, like presumably the first, was +/*bt*. If so, his father bred as *Ca* +/*Ca* +.

The two males must have started life with the constitution *Ca* +/+ *bt*, having inherited *Ca* from their mother and *bt* from their father. Now, if the order of genes is *Ca*—*bt*—centromere, then, in an animal of the constitution

$$\frac{Ca\text{—}+\text{—centromere}}{+\text{—}bt\text{—centromere}}$$

somatic crossing over between *Ca* and *bt* followed by equational separation of the centromeres will produce twin sectors as follows

$$\frac{Ca\text{—}+\text{—centromere}}{Ca\text{—}bt\text{—centromere}} \quad \text{and} \quad \frac{+\text{—}bt\text{—centromere}}{+\text{—}+\text{—centromere}}$$

The first of them corresponds to the gonadic tissue of male No. 1. Similarly, somatic crossing over between *bt* and the centromere will produce sectors

$$\frac{Ca\text{—}+\text{—centromere}}{Ca\text{—}+\text{—centromere}} \quad \text{and} \quad \frac{+\text{—}bt\text{—centromere}}{+\text{—}bt\text{—centromere}}$$

of which the first corresponds to the gonad of male No. 2. Perhaps in both instances the non-*Ca* sector failed to get into the skin, as the ♂♂ in question did not have any smooth-furred mosaic areas. If so, the case differs in this respect from the $W^v/+$ mosaic of Carter (1952) in which +/+ areas of the fur went with a W^v/W^v constitution in part of the gonad. However, as in the mouse wavy fur seems to force straight hair next to it into waves (Reed, 1938; Fraser, 1946), it is possible that some genetically non-*Ca* patches were present in the fur without being recognizable.

As already mentioned, male No. 2, when crossed to a *bt*/*bt* sister, produced twenty self and two belted offspring and thus clearly was not heterozygous for that gene. We have assumed above that the two belted young, like their self sibs, were +/*bt*.

As they have not been tested genetically, perhaps one or both of them may have been *bt/bt* after all. If so, this would indicate that a small part of the gonad of the male was derived from non-crossover cells.

On the interpretation given, the two ♂♂ breeding as *Ca/Ca* are independent somatic crossovers and thus a 'cluster' only in the sense that (? genetic) conditions favouring the occurrence of somatic crossing over must have been handed down to them by their parents.

Without the concept of somatic crossing over, the case just discussed is quite incomprehensible. Indeed, the original author (MacNeil, 1957) was driven to postulate the coincidence of two rare events to account for it. On the other hand, the case may be regarded as very strong evidence for the occurrence of somatic crossing over in the mouse.

(Note added 30 March 1965. Since this paper was submitted for publication, Professor G. Pontecorvo has kindly drawn my attention to the work of Klein & Klein (1964 and earlier papers) with the histocompatibility-2 (*H*-2) locus in the mouse which can best be accounted for on the basis of somatic crossing over. As tumours carrying a strong antigen of the *H*-2 locus will regress when transplanted into a mouse lacking it, tumour cells which have lost the antigen can be detected by a selective technique. Thus, if a tumour with antigen D is transplanted into a mouse without D, it will not establish itself, unless it contains a cell or cells from which D has been lost; the tumour derived from such a sector can subsequently be typed by suitable test sera. Now a tumour heterozygous for D and K in the *cis* phase (D K/– –, where – indicates the absence of the respective antigens) may either lose both D and K, or K alone, but it may not lose D and at the same time retain K. On the other hand, a tumour heterozygous for these two antigens in *trans* configuration (D –/– K) readily gives rise to cells which carry K, but not D. If the linear order is centromere – D – K, these facts can be explained most easily by somatic crossing over, but terminal deletion (much less probable on general grounds) is not ruled out. The findings of Klein & Klein (1964) thus lend further weight to the general argument of this paper.)

Somatic crossing over was first discovered in *Drosophila*, and there seems to be a widespread belief that somatic pairing which is peculiar to the *Diptera* is a necessary condition for its occurrence (for a recent discussion see Westergaard, 1964). However, somatic crossing over (or, more accurately, mitotic crossing over in organisms without a soma) has later been found in a variety of fungi like *Aspergillus*, *Penicillium* and others (Pontecorvo, 1958) in which there is certainly no more cytological evidence for somatic (mitotic) pairing than in the mouse. Evidently, in all organisms in which it has been found, conditions must exist during chromosome replication and mitosis which make the occasional occurrence of somatic crossing over possible. To what extent somatic pairing is one of these conditions is another question.

We shall now have to explore how much the concept of somatic crossing over can help in the understanding of the strange behaviour which some mammalian mutants have shown when they arose in the first instance.

4. MUTATIONS AT THE AGOUTI LOCUS

Mutations at this locus have been described many times in the mouse, and the agouti series at present includes no less than ten readily distinguishable alleles (A^{vy}, A^{v}, A^{w}, A, A^{i}, a^{td}, a^{t}, a^{z}, a and a^{e}). As the series includes light-bellied and dark-bellied agoutis (A^{w} and A) and light-bellied and dark-bellied non-agoutis (a^{t} and a) it was suspected early that there might be two linked genes, one responsible for pigmentation of the back, the other for that of the belly. As long ago as 1914, T. H. Morgan looked for recombinations between these hypothetical genes, but found none in a backcross of 180 animals. The mutations which have been observed in the agouti series are summarized in Table 1. The first instances (2 A/a offspring from A/A parents) were reported by Hagedoorn (1912). Little (1916) found two light-bellied agoutis (1 ♂, 1 ♀) in different F_2 families derived from a cross $A/A \times a/a$. A third A^{w} was found in the F_3 derived from the same cross, but in a family not descended from those which had produced similar animals in F_2. Altogether, there were 3 A^{w} animals in a total of 902 F_2 and F_3 mice, or about 1 in 300. In

Table 1. *Mutations at the agouti locus*

Author	Origin	Sex	Parents		Mutational step
Hagedoorn (1912)	Het.[1]	?	AA	AA	$A \rightarrow a$
Little (1916)	Het.	♂, ♀	Aa	Aa	$\begin{Bmatrix} a \rightarrow A^{w} \\ A \rightarrow A^{w} \end{Bmatrix}$
,, ,,	Het.	?	Aa	Aa	,,
,, ,,	Het.	♀	Aa	aa	,,
Pincus (1929*b*)	Inbr.	♀	aa	aa	$a \rightarrow a^{t}$
Keeler (1931)	Het.	♂	AA	$a^{t}a^{t}$	See text
Snell (1931)	Het.	♂	aa	aa	$a \rightarrow a^{t}$
,, ,,	Het.	♀	Aa	aa	$\left.\begin{matrix} \\ \\ \\ \end{matrix}\right\}$
,, ,,	Het.	?	Aa	$\begin{Bmatrix} Aa \\ aa \end{Bmatrix}$	$\begin{Bmatrix} a \rightarrow a^{t} \\ A \rightarrow a^{t} \end{Bmatrix}$
,, ,,	Het.	?	Aa	Aa	$\left.\begin{matrix} \\ \\ \\ \end{matrix}\right\}$
Little & Hummel (1947)	DBA[1]	?♀	aa	aa	$a \rightarrow A^{w}$
Bhat (1949)	Het.[2]	♀	aa	aa	$a \rightarrow A^{w}$
Hoecker (1950)	C58[2]	♂	aa	aa	$a \rightarrow A^{w}$
Wallace (1954)	Het.	♀	Aa^{t}	aa	See text
Hollander & Gowen (1956)	S × P[3]	♂	AA	aa	$A \rightarrow a^{e}$
Dahlberg (1959)	Brpb[4]	?	aa	aa	$a \rightarrow A^{w}$
Isherwood *et al.* (1960)	Inbr.	?	aa	aa	$a \rightarrow a^{t}$
Dickie (1962)	C3H	♀	AA	AA	$A \rightarrow A^{vy}$
Loosli (1963)	C57BL	?	aa	aa	$a \rightarrow a^{td}$

[1] Germinal mosaic (see Table 2).

[2] Germinal-somatic mosaic (see Table 2).

[3] *A/A father treated with 500 r. of X-rays and hence presumably an induced (spermatozoal) mutation; if it should have arisen spontaneously in the mother, the mutational step would be* $a \rightarrow a^{e}$.

[4] Parents treated with methylcholanthrene.

the same paper, Little mentions yet another mutation to A^w in a selection line maintained by repeated backcrosses $A/a \times a/a$ and in a total of about 400 animals. This is greatly in excess of an ordinary spontaneous mutation rate for a single gene, and the agouti locus seems to be particularly stable (Russell & Russell, 1959). As in similar crosses carried out previously, Little found no mutation to A^w in about 4500 animals, it appears that under certain (presumably genetical) conditions, the spontaneous mutability of the agouti locus may be considerably enhanced.

Most cases in Table 1 are 'reverse' mutations from recessive to more dominant alleles. As these are much more likely to be discovered soon after they have arisen than 'direct' mutations, the sample is heavily biased in their favour. Presumably it includes part only of the mutational steps possible at that locus.

By far the commonest mutations described are $a \rightarrow A^w$ (Little & Hummel, 1947; Bhat, 1949; Hoecker, 1950; Dahlberg, 1959) and $a \rightarrow a^t$ (Pincus, 1929*b*; Snell's (1931) first case; Isherwood *et al.*, 1960). The same two steps may be involved in the seven mutations at this locus described by Little (1916) and Snell (1931, cases 2–4) respectively. Counting the germinal mosaics as single events, fourteen out of twenty mutations are thus certainly or possibly ascribable to one or the other of these two mutational steps. Four other steps have occurred once each ($A \rightarrow a$; $A \rightarrow a^e$; $A \rightarrow A^{vg}$ and $a \rightarrow a^{td}$). The step $a \rightarrow A$ has so far only been observed in the rat (Grüneberg, 1937).

Perhaps the most intriguing case is the observation of Keeler (1931). To test the hypothesis of two separate loci for back and belly colour respectively, Keeler made a cross between ordinary grey-bellied agoutis (A/A) and black-and-tans (a^t/a^t); the F_1 was light-bellied agouti (A/a^t) and was backcrossed to non-agoutis (a/a). If a single gene only differentiates A from a^t, the backcross should produce only two phenotypes, grey-bellied agoutis (A/a) and black-and-tans (a^t/a) respectively. If there are two linked genes, crossing over should lead to the appearance of two additional phenotypes, light-bellied agouti and non-agouti respectively. With one exception, the F_1 mice produced only the two original phenotypes in agreement with the single-gene hypothesis. One exceptional F_1♂ mated to a/a ♀♀ produced nineteen light-bellied agoutis and thirteen dark-bellied non-agoutis, i.e., thirty-two 'crossovers' and no non-crossover. Using for the moment Keeler's notation (Aw = grey-bellied agouti; AW = light-bellied agouti; aw = dark-bellied non-agouti; and aW = light-bellied non-agouti or black-and-tan), and disregarding the possibility of mistaken identity, the F_1♂ in question was Aw/aW, but he transmitted to his offspring exclusively gametes which were AW and aw respectively. Five years before Stern's (1936) classical paper, Keeler considered the possibility of somatic crossing over. 'Such a crossover in the fertilized egg itself from which this male developed would account for his peculiarity but there is no ground for assuming such an unheard-of occurrence.' Having thus shied away from this original idea, Keeler then proceeded to give a different (and inadequate) interpretation of his case. 'Hence it seems probable that a mutation from w to W occurred in the parental gamete furnished by the agouti parent . . . or what seems less likely a reverse mutation from a to A in the parental gamete furnished

by the black-and-tan parent. . . .' As the first alternative would lead to the constitution AW/aW and the second to Aw/AW, neither would account for the breeding behaviour of the F_1♂ in question. Only simultaneous mutations in both parental gametes would do, a contingency too unlikely to be seriously considered.

On the other hand, Keeler's suggestion of somatic crossing over provides an adequate explanation of his case (Fig. 2).

The last case (Wallace, 1954) is a mating of the type A/a^t ♀ × a/a ♂ which produced thirty-five grey-bellied agoutis, twenty-nine black-and-tans and one a/a ♀. As discussed by the author, the exceptional animal can either be explained as a mutation from A or a^t to a, or as a crossover in the mother. In the latter case, it would be the same type of crossing over as that of Keeler, except that it would be meiotic rather than somatic.

More recently, convincing evidence has been produced which shows that the agouti locus of the mouse consists of mutational sites which can be separated by

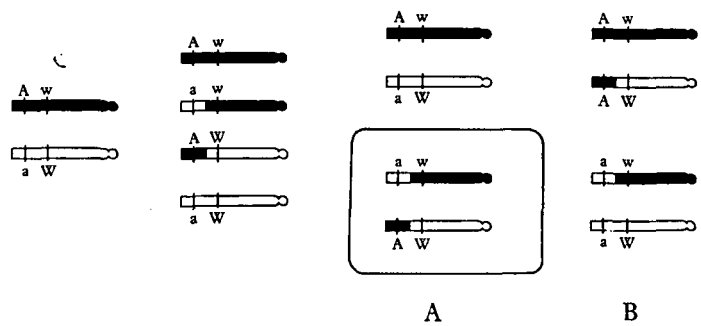

Fig. 2. Interpretation of Keeler's case in terms of somatic crossing over. It is assumed that the chromatids separated equationally according to modus A, and that the germinal epithelium was formed from descendants of the boxed cell.

crossing over (Russell, McDaniel & Woodiel, 1963). A new mutation a^x, from irradiated spermatogonia, in the a^x/a heterozygote causes a slightly paler belly; the a^x/a^x homozygotes die *in utero*. A balanced lethal stock $A^y/a^x \times A^y/a^x$, in a total of 1908 animals, produced four mice which were dark-bellied agouti rather than yellow, and one out of 260 tested yellows proved to be A^y/A rather than A^y/a^x. With the aid of the closely linked genes for kreisler (*kr*) and undulated (*un*) which straddle the agouti locus, it could be shown that two similar dark-bellied agouti exceptions were recombinants between a^x and A^y; the order of the genes is *kr* – a^x – A^y – *un*, and allowing for undetectable recombinants, the recombination frequency between a^x and A^y is 0·5%. As the authors also observed an agouti exception in a $A^y/a \times A^y/a$ mating, crossing over may also occur between these sites.

The experiments of Russell *et al.* (1963) leave no doubt that the agouti locus is 'complex', i.e., that it consists of mutational sites which can be separated by crossing over. The crossover frequency between a^x and A^y is of the same order of magnitude as the 'mutation rate' to A^w in Little's (1916) experiments; in the F_2 and F_3, A^w arose in A/a animals and may thus have been due to crossing over

rather than to mutation in the ordinary sense; the same may be true for the occurrence of A^w in the $A/a \times a/a$ selection line though in that case the possibility cannot be excluded that the mutation happened in an a/a animal.

In view of the evidence that the agouti locus is complex and that somatic crossing over occurs in the mouse, there is no reason to doubt the authenticity of Keeler's (1931) observation. Indeed, had he not boggled at the originality of his thought, he would have a claim to be regarded as one of Stern's forerunners in the discovery of somatic crossing over. In this connection it is worth mentioning that an exactly analogous case has been described, and interpreted in terms of somatic crossing over, by Muller as long ago as 1916. A *Drosophila* male which had inherited the two second chromosome recessives black and truncate from different parents transmitted these two genes (or their normal alleles) to its offspring exclusively in the coupling phase.

5. AUTOSOMAL MOSAICS DUE TO MUTATION

As discussed in some detail above, the mosaic patches in heterozygotes can best be accounted for by somatic crossing over. Mosaic spots in homozygotes must be due to mutation *sensu lato*. The nature of purely somatic patches will usually remain conjectural. An exceptional case has been described by Hoecker (1950) who, in a total of about 2000 mice of the C58 strain (which is a/a) found six mosaics with patches of banded and hence presumably agouti hairs; as the male with the

Table 2. *Autosomal germinal (G) and mixed (M = germinal-somatic) mosaics other than reversions*

Gene	Type of mutation	Type of mosaic	Sex	Stock of origin	Ratio of normal: mutant gametes	Ref.
Agouti	$A \rightarrow a$	G	?	Het.	6(?): 2	1
Albino	$+ \rightarrow c^-$	M	♂	$+/c^{ch}$	58:17*	2
Varitint-waddler	$+ \rightarrow Va$	G	?♀	?Het.	24: 2	3
Agouti	$a \rightarrow A^w$	G	?♀	DBA	18: 3	4
Agouti	$a \rightarrow A^w$	M	♀	Het.	61: 2	5
Agouti	$a \rightarrow A^w$	M	♂	C58	21: 3	6
Tail-short	$+ \rightarrow Ts$	G	♂	BALB/c	120: 8	7
Trembler	$+ \rightarrow Tr$	G	?	?Het.	5: 4	8
Crooked-tail	$+ \rightarrow Cd$	G	?♀	A	6: 2	9
Twirler	$+ \rightarrow Tw$	G	?	Het.	14: 2	10
Lurcher	$+ \rightarrow Lc$	G	♂	Het.	59: 3	11
Rib fusions	$+ \rightarrow Rf$	G	?	129	29: 2	12

* The mosaic transmitted 58 +, 71 c^{ch} and 17 c^- gametes.

References: 1, Hagedoorn (1912); 2, Dunn (1934); 3, Cloudman & Bunker (1945); 4, Little & Hummel (1947); 5, Bhat (1949); 6, Hoecker (1950); 7, Morgan (1950); 8, Falconer (1951); 9, Morgan (1954); 10, Lyon (1958); 11, Phillips (1960); 12, Mackensen & Stevens (1960).

most extensive such areas transmitted A^w to three out of twenty-four offspring (Table 2, ref. 6) and was thus a mixed (somatic and germinal) mosaic, the nature of the patches in the other five animals is not seriously in doubt; evidently, there is some genetically determined instability of the agouti locus in that stock. Two similar mixed mosaics have been described in the mouse (refs. 2 and 5, Table 2); though in all three instances the size of the mutant spots is roughly comparable, the involvement of the germinal epithelium is widely different. The remaining nine cases are ostensibly purely germinal. However, as in the last six of them a somatic sector if present would probably have little chance to manifest itself, it may be surmised that some of the 'germinal' mosaics may in reality be mixed. Similarly, the thirty or so mutations to dominant abnormal alleles (excluding the agouti locus) which have been reported in the mouse presumably include some germinal mosaics of which only one mutated gamete was recovered.

As in the mosaics of Table 2 the mutations must have happened in somatic cells, the question may be asked whether they may be explicable in terms of somatic crossing over. It is now widely believed that 'complex' genes are not the exception, but the rule; i.e., that genes generally consist of many sites (nucleotide pairs) which can mutate and which can be recombined by crossing over. Recombination at the agouti locus has been discussed above, and in at least one case (ref. 2, Table 2) where a new albino allele (c^-) arose in a $+/c^{ch}$ heterozygote, a similar interpretation may suggest itself. It may be surmised that recombination between different iso-alleles may give rise to 'synthetic' mutant genes. Four and possibly six of the stocks in which the mosaics arose were sufficiently heterogeneous genetically to make the presence of different wild-type, etc., iso-alleles plausible. But in five instances the mosaics occurred in well-established inbred strains in which different iso-alleles will be present only exceptionally as the result of a recent mutation. It must be concluded that although somatic crossing over may account for a few of the mutational mosaics, this cannot be the case for all of them. By implication, this also applies to the 'sporadic' mutations. Over one-third of them arose in well-established inbred strains. On the other hand, there are a number of instances which may well be explicable in terms of somatic crossing over. Thus the brown allele cordovan (b^c) occurred in the F_1 of a cross DBA × C57BL, i.e., a cross of the type $b/b \times +/+$ (Miller & Potas, 1955), and Himalayan dilution (c^h) similarly in the F_1 of a cross DBA × AKR, i.e., of the type $+/+ \times c/c$ (Green, 1961). There are two other instances where mutants first arose in F_1 generations involving two inbred strains (White, Mi^{wh}, Grobman & Charles, 1947; and Opossum, Green & Mann, 1961). Whereas these and similar cases are obviously open to other interpretations, somatic crossing over in an early cleavage division is a possible explanation.

For sake of completeness, we mention here two mutational mosaics in other rodents. In the rat, a germinal mosaic to a darker allele of hooded was recorded by Castle & Phillips (1914); two mutant individuals (1♂, 1♀) were sired by a single male with two different females, presumably along with many normal young. In the guinea pig, Wright & Eaton (1926) described a mixed somatic and germinal

mosaic ♂ which started life as c^d/c^d; he had two large intensely coloured coat areas, one anteriorly and one posteriorly; he transmitted altogether 79 + and 149 c^d gametes which corresponds to about 70% $+/c^d$ and 30% c^d/c^d germinal epithelium.

6. SEX-LINKED MUTATIONS IN THE MOUSE

With two exceptions, the early history of the sex-linked mutations in the mouse is unremarkable. Tabby (*Ta*) first appeared as a ♂ which had twenty normal brothers (Falconer, 1953), and Bent-tail (*Bn*) similarly appeared as a single ♂ in a litter of seven, with all subsequent litters of the same parents normal (Garber, 1952). The genes for Tortoiseshell (*To*; Dickie, 1954), jimpy (*jp*; Phillips, 1954) and Striated (*Str*; Phillips, 1963) first appeared as single ♀♀ heterozygous for these genes, the latter following X-ray treatment of the father.

One observation concerning jimpy which now has a familiar ring is worth relating. Jimpy ♂♂ suffer from a neurological disorder which includes intention tremor and later usually epileptiform convulsions; they die between 20 and 40 days, usually around 28 days of age. The gene is completely recessive in $+/jp$ ♀♀, and as *jp* ♂♂ never live to breeding age, the occurrence of jimpy ♀♀ is not expected. Nevertheless, from a mating $+/jp$ ♀ × *Ta* ♂, a phenotypically jimpy female was obtained (Phillips, 1954). As she had inherited *jp* from her mother and *Ta* from her father, she could not be an *XO* female; she died at the age of 31 days, and her internal genitalia were typically female. Of the five possible explanations considered by the author, that of somatic crossing over seems by far the most plausible to the present writer. Evidently, part, at least, of the central nervous system had become *jp*/*jp* so that the gene could manifest itself in a female.

The two exceptional cases both involved the locus of Brindled and Mottled which are very probably alleles. Brindled (Mo^{br}; Fraser, Sobey & Spicer, 1953) arose as a single ♀ in the inbred strain C57BL; affected ♀♀ are irregularly mottled with off-white areas rather finely interspersed with fully-coloured fur. The ♂♂ almost invariably die between 10 and 14 days; they are a uniform rather dirty white colour. The gene for Mottled (*Mo*; Fraser, Sobey & Spicer, 1953) similarly arose as a single female in a genetically heterogenous stock; she had seventy-six normal (non-albino) sibs. Phenotypically, *Mo*/+ ♀♀ are similar to $Mo^{br}/+$ ♀♀. However, *Mo* ♂♂ differ from Mo^{br} ♂♂ in perishing as 11-day embryos (Falconer, 1953). It has been suggested by Lyon (1961) that the mottled phenotype of *Mo*/+ and $Mo^{br}/+$ ♀♀ (like similar irregular patterns in *To*/+, *Ta*/+ and *Str*/+ ♀♀ or in tortoiseshell cats) may be explained in the following way. In the body cells of mammalian females, only one of the two X-chromosomes is functional; during development, inactivation once effected is irreversible with the result that the coat of a $Mo^{br}/+$ ♀ ultimately consists of a patchwork of $(Mo^{br})/+$ (fully-coloured) and $Mo^{br}/(+)$ (off-white) areas. By contrast, in Mo^{br} ♂♂ which have only a single X-chromosome, the fur is off-white throughout. On this hypothesis, the *Mo* ♂♂, if they lived to grow fur, should have a uniformly off-white coat like the Mo^{br} ♂♂, but they should not be mottled.

The two exceptional cases are very similar to each other. One mutant is indistinguishable from *Mo* and probably a recurrence of that gene (Lyon, 1960; the name Dappled originally given to this gene was subsequently withdrawn); the other is a mutation to a distinguishable allele, called Dappled (*Mo*^{dp}, Phillips, 1961). The origin of the first of these is described by Lyon as follows.

The original mutant animal was a male, which was found among the offspring of the control series of a mutagenesis experiment. Phenotypically this animal resembled his later female descendants. His coat was mottled with patches of white, light-colored and full-colored hairs, and also with intermingled hairs of different colors, and his vibrissae were curly. He was mated to several normal females and sired 187 offspring, 95 normal males and 92 females of which 19 were dappled like himself. His dappled offspring when mated to normal males produced dappled females, normal females and normal males in approximately equal numbers, while his normal offspring produced only normal young.

The origin of Dappled (*Mo*^{dp}) is described by Phillips (1961) as follows.

The mutation first appeared in an F_1 male from [a] low-dosage γ-irradiation experiment . . .; the parents of this animal produced one Dappled male out of 64 classified offspring. On outcrossing to unrelated females, he sired 10 Dappled females, phenotypically similar to himself, 278 normal females and 290 normal males. The 10 Dappled females were all sired in the first 4 weeks of a total breeding life of 46 weeks.

As in the preceding case, the *Mo*^{dp}/+ ♀♀ subsequently segregated perfectly normally. The breeding behaviour of both animals shows that they must have been mixed somatic and germinal mosaics; the former produced about twenty-one, the latter about 3% mutant spermatozoa. The odd feature of both males is that phenotypically they resembled their heterozygous daughters. The two males were mottled because some of their coat areas were genetically + whereas others were *Mo* or *Mo*^{dp} respectively; if their coats had been genetically uniform (i.e., either *Mo* or *Mo*^{dp}), their coat colour presumably would have been off-white throughout. The females, by contrast, according to the Lyon hypothesis, are mottled by virtue of gene inactivation; genetically the whole of their coat is *Mo*/+ and *Mo*^{dp}/+ respectively. Somewhat to my chagrin, I cannot discover a connection of these two anomalous cases with the main topic of this paper. In itself, the occurrence of a somatic mutation to a sex-linked lethal gene in a male is not a very surprising event. What is surprising is that the somatic mutation should in both cases have resulted in a pattern of mosaicism so like that of the normal heterozygous females brought about by a totally different mechanism.

7. REVERSIONS

We mention here briefly three investigations which have so far only been reported in abstract form. All of them deal with phenomena which are too frequent to be easily accommodated in the conceptual framework of ordinary gene mutations.

Schaible & Gowen (1960) report on reversions to wild-type (intense) coloration which occur in *Mi*^{wh}/+, *W*^{a}/+ and *Va*/+ heterozygotes respectively. Whether these mosaics are purely somatic is difficult to tell as in such heterozygotes only large mutated sectors of the gonad (as in Carter's *W*^{v}/+ mosaic) would be detectable.

The other two cases involve reversions to normal in recessive homozygotes. Russell & Major (1956) report such events in a homozygous pearl (*pe*/*pe*) stock. Small mosaics are invariably purely somatic, but five large mosaics have involved both somatic and germinal material. The authors considered the possibility that the reversions might be due to somatic crossing over between pseudoalleles at the pearl locus, but as the pearl stock was already somewhat inbred, they considered somatic reverse mutations as more likely.

Finally, there is a report (Glenn-Wolfe, 1963) on reversions to wild-type which occur in p'/p' homozygotes (p' is an unstable allele of ordinary pink-eyed dilution, p). Somatically, the mosaics vary from a few dark hairs to heavy mottling, and the germinal epithelium may be involved.

Pending fuller publication, speculation on these interesting conditions would be premature.

8. CONCLUDING REMARKS

On account of their rarity, the phenomena discussed in this paper are not readily accessible to planned experimentation. The interpretation of facts after the event is always rather speculative. However, the shortcomings of the historical approach are somewhat tempered by the fact that certain assumptions which have been made are open to verification or falsification. For instance, to be explicable in terms of somatic single crossing over, the order of genes in linkage group 1 of both rat and mouse should be *p*—*c*—centromere; if the alternative order is true, this would require recourse to double crossing over which would weaken (though not necessarily destroy) the argument. The same applies to the order *Ca*—*bt*—centromere in linkage group 6. Similarly, if it should be found that in the rabbit the gene for *d* is located close to the centromere, this would be incompatible with our interpretation, as, in the absence of localization of chiasmata, only a gene which is far from the centromere will readily become homozygous as the result of somatic crossing over.

In view of the diverse nature of the phenomena which can be accounted for in terms of somatic crossing over in the laboratory rodents, the present author feels that there is a strong case for its occurrence.

SUMMARY

A review is given of published accounts of mosaics in mice and other rodents, of mutations and of certain unexplained events. The cumulative weight of evidence makes a strong case for the existence of somatic crossing over in the laboratory rodents.

REFERENCES

BHAT, N. R. (1949). A dominant mutant mosaic house mouse. *Heredity, Lond.* **3**, 243–248.

BILLINGHAM, R. E. & SILVERS, W. K. (1960). The melanocytes of mammals. *Q. Rev. Biol.* **35**, 1–40.

CARTER, T. C. (1952). A mosaic mouse with an anomalous segregation ratio. *J. Genet.* **51**, 1–6.

CASTLE, W. E. (1922). On a non-transmissible tri-color variation in rats. *Carnegie Inst. Wash.*, Publ. No. 320, pp. 51–54.

CASTLE, W. E. (1929). A mosaic (intense-dilute) coat pattern in the rabbit. *J. exp. Zool.* **52,** 471–480.

CASTLE, W. E., GATES, W. H., REED, S. C. & SNELL, G. D. (1936). Identical twins in a mouse cross. *Science, N.Y.* **84,** 581.

CASTLE, W. E. & PHILLIPS, J. C. (1914). Piebald rats and selection. *Carnegie Inst. Wash.*, Publ. No. 195, pp. 54.

CLOUDMAN, A. M. & BUNKER, L. E., JR. (1945). The varitint-waddler mouse. A dominant mutation in *Mus musculus*. *J. Hered.* **36,** 259–263.

CURTIS, M. R. & DUNNING, W. F. (1940). An independent recurrence of the blue mutation in the Norway rat and a blue-black mosaic. *J. Hered.* **31,** 219–222.

DAHLBERG, J. (1959). A reverse mutation in the house mouse. *J. Hered.* **50,** 248–252.

DICKIE, M. M. (1954). The tortoise shell house mouse. *J. Hered.* **45,** 158, 190.

DICKIE, M. M. (1962). A new viable yellow mutation in the house mouse. *J. Hered.* **53,** 84–86.

DUNN, L. C. (1934). Analysis of a case of mosaicism in the house-mouse. *J. Genet.* **29,** 317–326.

FALCONER, D. S. (1951). Two new mutants, 'Trembler' and 'reeler', with neurological actions in the house mouse (*Mus musculus* L.). *J. Genet.* **50,** 192–201.

FALCONER, D. S. (1953). Total sex-linkage in the house mouse. *Z. indukt. Abstamm.- u. VererbLehre,* **85,** 210–219.

FANKHAUSER, G. & HUMPHREY, R. R. (1954). Chromosome number and development of progeny of triploid axolotl males crossed with diploid females. *J. exp. Zool.* **126,** 33–58.

FELDMAN, H. W. (1935). A mosaic (dark-eyed intense-pink-eyed dilute) coat colour of the house mouse. *J. Genet.* **30,** 383–388.

FISHER, R. A. (1929). Note on a tricolour (mosaic) mouse. *J. Genet.* **23,** 77–81.

FRASER, A. S., SOBEY, S. ; & SPICER, C. C. (1953). Mottled, a sex-modified lethal in the house mouse. *J. Genet.* **51,** 217–221.

FRASER, F. C. (1946). The expression and interaction of hereditary factors producing hypotrichosis in the mouse: histology and experimental results. *Can. J. Res.* D, **24,** 10–25.

GARBER, E. D. (1952). 'Bent-tail', a dominant, sex-linked mutation in the mouse. *Proc. natn. Acad. Sci. U.S.A.* **38,** 876–879.

GLENN-WOLFE, H. (1963). Two unusual mutations affecting pigmentation in the mouse. *Proc. XI Intern. Congr. Genet.* (The Hague), **1,** 251 (Abstr.).

GREEN, E. L. & MANN, S. J. (1961). Opossum, a semi-dominant lethal mutation affecting hair and other characteristics of mice. *J. Hered.* **52,** 223–227.

GREEN, M. C. (1961). Himalayan, a new allele of albino in the mouse. *J. Hered.* **52,** 73–75.

GRELL, SISTER MARY (1946). Cytological studies in *Culex*. I and II. *Genetics,* **31,** 60–76, 77–94.

GROBMAN, A. B. & CHARLES, D. R. (1947). Mutant white mice. A new dominant autosomal mutant affecting coat color in *Mus musculus*. *J. Hered.* **38,** 381–384.

GRÜNEBERG, H. (1937). A reverse mutation in the rat (*Mus norvegicus*). *J. Genet.* **35,** 177–181.

HAGEDOORN, A. L. (1912). The genetic factors in the development of the house mouse which influence coat colour. *Z. indukt. Abstamm.- u. VererbLehre,* **6,** 97–136.

HOECKER, G. (1950). Mutaciones dominantes reversivas en mosaico en la cepa pura de ratones C_{58} negra. *Biológica, Santiago,* **12,** 25–37.

HOLLANDER, W. F. & GOWEN, J. W. (1956). An extreme non-agouti mutant in the mouse. *J. Hered.* **47,** 221–224.

HUSKINS, C. L. (1948). Segregation and reduction in somatic tissues. I. Initial observations in *Allium cepa*. *J. Hered.* **39,** 311–325.

ISHERWOOD, J. E., STRONG, L. C. & QUEVEDO, W. C., JR. (1960). A new mutation of *a* to *a* in the mouse. *J. Hered.* **51,** 121, 135, with a correction on p. 166.

KEELER, C. E. (1931). A probable new mutation to white-belly in the house mouse, *Mus musculus*. *Proc. natn. Acad. Sci. U.S.A.* **17,** 700–703.

KLEIN, E. & KLEIN, G. (1964). Studies on the mechanism of isoantigenic variant formation in heterozygous mouse tumours. III. Behavior of *H*-2 antigens D and K when located in the *trans* position. *J. natn. Cancer Inst.* **32,** 569–578.

LITTLE, C. C. (1916). The occurrence of three recognized color mutations in mice. *Am. Nat.* **50**, 335–349.

LITTLE, C. C. & HUMMEL, K. P. (1947). A reverse mutation to a 'remote' allele in the house mouse. *Proc. natn. Acad. Sci. U.S.A.* **33**, 42–43.

LOOSLI, R. (1963). Tanoid—a new agouti mutant in the mouse. *J. Hered.* **54**, 26–29.

LYON, M. F. (1958). Twirler: a mutant affecting the inner ear of the house mouse. *J. Embryol. exp. Morph.* **6**, 105–116.

LYON, M. F. (1960). A further mutation of the mottled type in the house mouse. *J. Hered.* **51**, 116–121.

LYON, M. F. (1961). Gene action in the X-chromosome of the mouse (*Mus musculus* L.). *Nature, Lond.* **190**, 372–373.

MACKENSEN, J. A. & STEVENS, L. C. (1960). Rib fusions, a new mutation in the mouse. *J. Hered.* **51**, 264–268.

MACNEIL, M. (1957). Two different rare events occurring simultaneously in the house mouse. *Heredity, Lond.* **11**, 261–264.

MILLER, D. S. & POTAS, M. Z. (1955). Cordovan, a new allele of black and brown color in the mouse. *J. Hered.* **46**, 293–296.

MORGAN, T. H. (1914). Multiple allelomorphs in mice. *Am. Nat.* **48**, 449–458.

MORGAN, W. C. (1950). A new tail-short mutation in the mouse whose lethal effects are conditioned by the residual genotypes. *J. Hered.* **41**, 208–215.

MORGAN, W. C. (1954). A new Crooked tail mutation involving distinctive pleiotropism. *J. Genet.* **52**, 354–373.

MORGAN, W. C. & HOLMAN, S. P. (1955). Eight mosaic mice in thirty years. *J. Hered.* **46**, 47–48.

MULLER, H. J. (1916). The mechanism of crossing-over. II. *Am. Nat.* **50**, 284–305.

PHILLIPS, R. J. S. (1954). *Jimpy*, a new totally sex-linked gene in the house mouse. *Z. indukt. Abstamm.- u. VererbLehre.* **86**, 322–326.

PHILLIPS, R. J. S. (1960). 'Lurcher', a new gene in linkage group XI of the house mouse. *J. Genet.* **57**, 35–42.

PHILLIPS, R. J. S. (1961). 'Dappled', a new allele at the *Mottled* locus in the house mouse. *Genet. Res.* **2**, 290–295.

PHILLIPS, R. J. S. (1963). *Striated*, a new sex-linked gene in the house mouse. *Genet. Res.* **4**, 151–153.

PICKARD, J. N. (1929). A brown-and-black rabbit. A possible case of somatic segregation. *J. Hered.* **20**, 483–484.

PICKARD, J. N. (1936). A black-blue Dutch rabbit. *J. Genet.* **33**, 337–341.

PINCUS, G. (1929*a*). A mosaic (black-brown) coat pattern in the mouse. *J. exp. Zool.* **52**, 439–441.

PINCUS, G. (1929*b*). A spontaneous mutation in the house mouse. *Proc. natn. Acad. Sci. U.S.A.* **15**, 85–88.

PONTECORVO, G. (1959). *Trends in Genetic Analysis*, pp. X + 145. New York and London: Columbia U.P. and Oxford U.P.

REED, S. C. (1938). Determination of hair structure. I. The production of waved hair from genetically non-waved cells. *J. exp. Zool.* **79**, 347–354.

ROBINSON, R. (1956). A review of independent and linked segregation in the rabbit. *J. Genet.* **54**, 358–369.

RUSSELL, L. B., MCDANIEL, M. N. C. & WOODIEL, F. N. (1963). Crossing-over within the *a* 'locus' of the mouse. *Genetics*, **48**, 907 (Abstr.).

RUSSELL, L. B. & MAJOR, M. H. (1956). A high rate of somatic reversion in the mouse. *Genetics*, **41**, 658 (Abstr.).

RUSSELL, L. B. & MAJOR, M. H. (1957). Radiation-induced presumed somatic mutations in the house mouse. *Genetics*, **42**, 161–175.

RUSSELL, W. L. & RUSSELL, L. B. (1959). The genetic and phenotypic characteristics of radiation-induced mutations in mice. *Radiat. Res.* Suppl. 1, 296–305.

SCHAIBLE, R. H. & GOWEN, J. W. (1960). Delimitation of coat pigment areas in mosaic and piebald mice. *Genetics*, **45**, 1010 (Abstr.)

SNELL, G. D. (1931). Inheritance in the house mouse, the linkage relations of short-ear, hairless, and Naked. *Genetics*, **16**, 42–74.

STERN, C. (1936). Somatic crossing over and segregation in *Drosophila melanogaster*. *Genetics*, **21**, 625–730.

STEVENS, W. L. (1937). A test for uniovular twins in mice. *Ann. Eugen.* **8**, 70–73.

WALLACE, M. E. (1954). A mutation or a crossover in the house mouse? *Heredity*, **8**, 89–105.

WESTERGAARD, M. (1964). Studies on the mechanism of crossing over. I. Theoretical considerations. *C. r. Trav. Lab. Carlsberg*, **34**, 359–405.

WRIGHT, S. & EATON, O. N. (1926). Mutational mosaic coat patterns of the guinea pig. *Genetics*, **11**, 333–351.