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Attempts to test the inactive-X theory of dosage compensation in mammals

By MARY F. LYON
Medical Research Council Radiobiological Research Unit, Harwell, Berkshire, England

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The inactive-X theory postulates that the normal method of dosage compensation in mammals is inactivation of one X chromosome of females early in embryonic development (Lyon, 1961, 1962; Beutler, Yeh & Fairbanks, 1962). This means that normal adults of both sexes have in effect only a single dose of X-linked genes, and provides an explanation for the fact that normal males and females appear to have equal amounts of the gene products of X-linked genes such as those for anti-haemophilic globulin and glucose-6-phosphate-dehydrogenase activity in man (Beutler, Yeh & Fairbanks, 1962; Grumbach, Marks & Morishima, 1962). The theory also explains the mosaic phenotype of female mammals heterozygous for sex-linked colour genes. Early in embryonic development either one of the two X chromosomes is inactivated at random in each of the future pigment cells. Multiplication during development leads to whole patches of cells in the adult descended from a single one at the time of inactivation. Those with the mutant gene inactive give rise to a normal-coloured patch, and vice versa (Text-fig. 1).

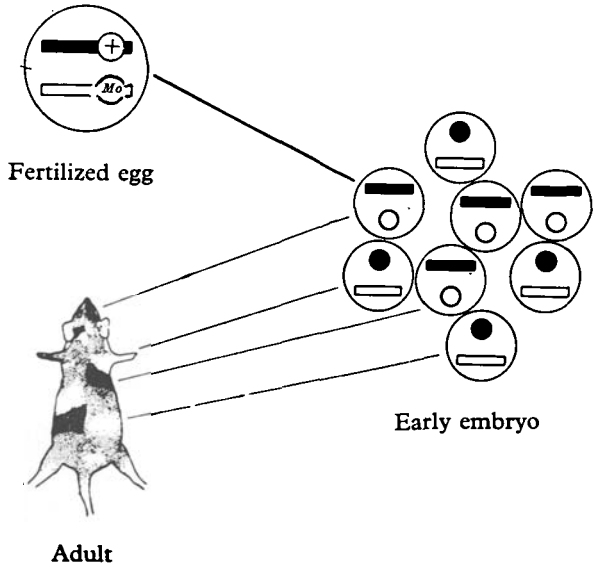

Fig. 1. Diagrammatic representation of the inactive-X theory. The inactive-X is represented as circular, and the active one as rod-shaped.

Various expectations can be formulated from the theory and used to test it. One such expectation concerns the phenotype of females heterozygous for two non-allelic X-linked genes acting through the same cells. If the mutant genes are carried on opposite X chromosomes then all cells should have either one or the other mutant acting and there should be no patches in which both or neither are acting. Conversely, if the two mutants are carried on the same X then all cells should have either both mutants acting or neither. The present paper describes attempts to test this expectation by means of breeding experiments with mice.

1. PLAN OF EXPERIMENTS

(i) *Choice of mutants*

The effect described above will only be detectable if the genes concerned have an action that is both visible and localized, and if the gene product is not diffusible. One obviously suitable group of mutants are the colour mutants. There is then the further requirement that the colours produced by the chosen mutants should be clearly distinguishable both from each other and from wild-type. Of the known sex-linked colour mutants of the mouse, only one, *blotchy* (*Blo*) (Russell & Saylors, 1962), is viable and fertile in the male. Unfortunately, the colour produced by this mutant is such that at weaning age heterozygous females are sometimes difficult to distinguish from wild-type (Russell, 1960), and so it was considered unsuitable. It was therefore necessary to use autosomal colour genes translocated on to the X. Cattanach (1961) described a translocation in which part of the autosomal linkage group I, including the wild-type alleles of the albino series (c, c^{ch}, etc.) and pink-eyed dilution (p), had been translocated to the X-chromosome. Females heterozygous for the translocation and carrying the colour mutants concerned on their normal autosomes were 'flecked' with patches of mutant and wild-type colour. Cytological studies by Ohno & Cattanach (1962) and Ford (1962) have shown that these animals have an autosomal fragment inserted into the X chromosome. Thus, this translocation potentially provides two more colour mutants for crossing with suitably distinguishable sex-linked colour genes. The colour produced by the mutant pink-eye is easily distinguishable both from wild-type, and from that produced by the sex-linked mutant *dappled*, Mo^{dp} (Phillips, 1961). Since males carrying the translocation are usually fertile it was possible to devise a suitable cross to produce females carrying dappled on one X, and the wild-type allele of pink-eye on the other. It was obviously important to try to make the tests with as many different pairs of sex-linked genes as possible and therefore another similar cross was made using the albino alleles, although in this case the colours, though distinguishable, were not as easily so as with pink-eye.

Another group of mutants which would be expected to give the effect are those with a localized effect on hair structure. One of these is *tabby* (*Ta*), which in males results in absence of zigzag and guard hairs from the coat, and in females gives a striped effect due to the presence of mutant and normal coat patches (Falconer, 1953, and Table 3). *Tabby* was crossed with *striated* (*Str*) (Phillips, 1963), which produces short patches in the fur of heterozygous females, and is lethal in the male.

Yet further crosses were made between *tabby* and *dappled*. In this case the two genes concerned acted on different characters, coat texture and hair pigment, and this cross was intended as a type of control, to test the expectation that it is only when two sex-linked genes act through the same cells that their action in double heterozygotes is alternate, and that otherwise the two sets of patches caused by the two genes are distributed at random.

(ii) *Breeding methods and results*

In each case the first crosses made were designed to produce females carrying the two genes concerned on opposite X chromosomes, the repulsion heterozygotes. From these, further crosses were then made to obtain the complementary type with the two genes on the same X.

(iii) *Crosses to obtain repulsion heterozygotes*

(*a*) *Dappled and pink-eye*

Text-fig. 2 gives a plan of the cross used to produce females carrying the mutant dappled on one X and the wild-type allele of pink-eye on the other. Dappled females homozygous for pink-eye were crossed with males having Cattanach's translocation and also carrying pink-eye. (Such males are wild-type in colour

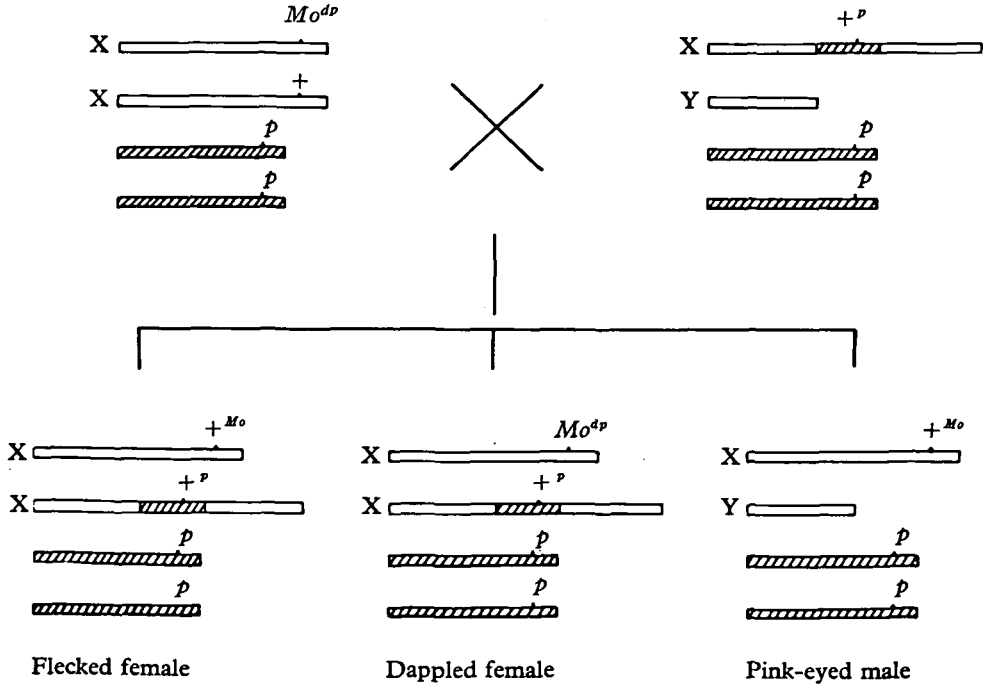

Fig. 2. Plan of the cross used to obtain repulsion heterozygotes for dappled and Cattanach's translocation (an insertion into the X chromosome). The colours of the animals are shown in Plate 1.

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since the single X, carrying the $+^p$ allele, is active in all cells.) All the female offspring were expected to carry the translocation, and half of these also carried dappled on their maternal X chromosome. The dappled young were picked out by the curly whiskers which the mutant produces, and examined carefully for patches of pink-eye colour. (Table 1 gives a list of expected colours.) Fifteen such females have been found (Table 2); all showed typical white dappled markings and none showed any patches of *pp*. A representative one of them is shown in Plate I.

Table 1. *Colours of patches expected in double heterozygotes for Cattanach's translocation*

Gene acting	Coat colour	Expected on inactive-X theory	
		$Mo^{dp}+/+fd$	$Mo^{dp}fd/++$
Mo^{dp} only	White	+	−
*fd** only	Wild-type	+	−
Both Mo^{dp} and *fd*	White	−	+
Neither Mo^{dp} nor *fd*	Pink-eye or light chinchilla	−	+

* Cattanach (1961) uses the symbol *fd* (flecked) to represent the translocation.

Table 2. *Offspring of crosses to obtain repulsion heterozygotes for dappled and Cattanach's translocation*

Parents	Offspring		
	Female		Male
	$Mo^{dp}+/+fd$ dappled	$++/+fd$ flecked	$++$ pink-eye or chinchilla
$Mo^{dp}+\ pp♀ \times fd\ pp♂$	15	21	7
$Mo^{dp}+\ c^{ch}c^{ch}♀ \times fd\ c^{e}c♂$	14	18	38

One of the first four females died when $3\frac{1}{2}$ weeks old; the remaining three were genetically tested and their presumed genotype $Mo^{dp}+/+fdpp$ was confirmed (see below).

(*b*) *Dappled and chinchilla*

A similar type of cross using dappled females homozygous for chinchilla, and a male with Cattanach's translocation, was made to produce dappled females carrying the wild-type allele of chinchilla on the opposite X chromosome, and to observe these for patches of light chinchilla colour. The crosses were so arranged that the colour to be detected should be light chinchilla (cc^{ch} or $c^{e}c^{ch}$) rather than chinchilla ($c^{ch}c^{ch}$) since the former is more easily distinguishable from wild-type. Neither

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A. Heterozygous dappled female, $Mo^{dp}+$, showing white markings on wild-type background.
B. Dappled pink-eyed female, $Mo^{dp}+pp$, with white markings against background of pp colour.
C. Flecked female heterozygous for Cattanach's translocation, $fd+pp$, and carrying pp on her autosomes like female B. Only small patches of pp colour are visible, and large patches of a darker colour due to the action of the wild-type allele of p, inserted into the X chromosome. The animal is also homozygous for the autosomal colour mutant, brown bb, which gives the non-pink parts a brown hue ($+^p bb$).
D. Repulsion heterozygote for dappled and Cattanach's translocation, $Mo^{dp}+/+fd$, homozygous for pp and bb on her autosomes. She shows patches of white, due to Mo^{dp}, as in B, and of $+^p bb$ due to the translocation, as in C, but shows none of the pp colour.

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light chinchilla nor chinchilla, however, is as easily distinguishable from the intermediate colour of dappled as is pink-eye.

Fourteen dappled females have been observed in the progeny of these crosses (Table 2) and none has shown any definite light chinchilla patches.

As in the crosses with pink-eye, tests are being made to confirm the genotype of these females, which are expected to be $Mo^{dp}+/+fd\,cc^{ch}$ or $c^e c^{ch}$.

(*c*) *Tabby and striated*

Preliminary studies with striated. The mutant *striated* was first recognized by the striped effect in female heterozygotes, similar to that of tabby heterozygotes. However, Phillips (1963) showed that striated was not allelic with tabby, but linked to it, giving about 15% recombination with *Ta* and 34% with *bent-tail*, *Bn*. It was thus a second sex-linked mutant with a localized effect on hair growth.

Striated heterozygotes, kindly provided by Miss Phillips, were examined to find the cause of the striped effect. When the fur was stroked backwards from tail to neck patches of short fur could be seen. These patches were irregular in size and shape, not necessarily running in transverse stripes across the body. When the fur was smoothed back into its normal position all but the largest of these patches became invisible, through being covered by the long hair growing immediately anterior. A transverse stripe was, however, formed just behind the patch because of the break, at hair-tip level, in the normal smooth anteroposterior succession of hairs. The yellow tips of the short hairs did not, as is usual, cover the dark base of the hairs behind them, so that a dark line was visible. As would be expected, no such effect was produced in a direction parallel to the growth of the hairs, i.e. there were no anteroposterior stripes but only transverse ones.

Hairs were plucked from the short and normal-length regions and examined under a stereoscopic microscope. The hairs were classified into the usual four types found in the mouse: zigzags, awls, auchenes and guard hairs (Table 3). In the short regions very few auchenes or guard hairs were found, but the zigzags and awls were in an approximately normal ratio to each other. Many of the awls were slightly curved, rather than straight as in normal mice, and some zigzags had fewer kinks than normal. The mean length of ten zigzag hairs measured was 4·08 mm. compared with 5·93 mm. for a similar sample of ten zigzags from a normal region.

Thus, these studies showed that the two mutants tabby and striated both produced distinct and clearly recognizable localized effects on coat structure and formed a suitable pair for study of the phenotype of double heterozygotes. Female offspring of the cross $Str+\ +\ +♀\times +\ Ta♂$ were examined. All were expected to carry *Ta* and all were in fact visibly striped. Those in which patches of short fur could be found by stroking the coat backwards were considered to carry *Str* and therefore to be double heterozygotes, $Str+/+Ta$. Hair samples from these and from an equal number of $+\ +/+Ta$ sisters were studied. As Table 4 shows, samples plucked from the short patches, where *Str* was acting, were expected to have normal proportions of zigzag hairs, whereas those from normal length regions were expected to have a proportion of zigzags equal to that found in the abnormal regions of $Ta+$

Table 3. *Hair counts from offspring of crosses involving tabby and striated*

Source of animals	Genotype	No. mice	Sample region	No. of hairs				% zigzag hairs
				Zigzag	Awl	Auchene	Guard hair	
Preliminary studies	*Str*/+	3	Short	85	45	1	1	64·4
			Normal length	74	28	6	1	67·9
Crosses to obtain repulsion heterozygotes	*Ta*+	9	Stripe	44	476	5	5	8·3
			Normal	255	240	20	5	49·0
	Str+/+*Ta*	9	Short	417	219	14	5	63·7
			Normal length	124	503	11	9	19·2
Crosses to obtain coupling heterozygotes	*Ta*+	10	Stripe	79	734	6	—	9·6
			Normal	367	225	10	1	60·9
	Str/+	36	Short	1908	884	5	3	68·1
			Normal length	1396	537	63	11	69·6
	StrTa/++	2	Short	9	317	9	1	2·7
			Normal length	205	73	13	6	69·0

The results from *Str*+ and *Ta*+ indicate that *Str* has no effect on percentage of zigzag hairs (last column) whereas *Ta* causes a marked reduction. Comparison of the short and normal length hairs in *Str*+/+*Ta* and *StrTa*/++ shows in which regions *Ta* is acting.

heterozygotes. The first expectation was completely fulfilled (Table 3), showing that *Ta* had no effect where the gene *Str* was acting. The proportion of zigzags in the normal length patches was somewhat higher than that in the abnormal regions of *Ta*+, suggesting that *Ta* was not acting fully. However, there was much vari-

Table 4. *Expected effect of the action of the genes tabby and striated in double heterozygotes*

Gene acting	Hair length	Hair population	Expected on inactive-X theory	
			Str+/+*Ta*	*StrTa*/++
Tabby	Normal	Few zigzags	+	−
Striated	Short	Normal	+	−
Both *Ta* and *Str*	Short	Few zigzags	−	+
Neither *Ta* nor *Str*	Normal	Normal	−	+

ation between individual $Ta+$ animals in this proportion (range from 0 to about 30%), and since the results with tabby and striated otherwise agreed well with the theory this small difference was not considered important.

(d) Dappled and tabby

Heterozygous dappled females, $Mo^{dp}+$, were mated to tabby males. Half the female offspring were expected to carry dappled on one X and tabby on the other, being $Mo^{dp}+/+Ta$. If the two genes acted through the same cells then Ta would be expected not to act in the white patches of the coat where Mo^{dp} was acting, and to act fully in the dark patches. On the other hand, if Mo^{dp} and Ta acted through different cells then in some Mo^{dp} patches Ta would also act. Hair samples were taken from white and pigmented coat areas and examined for the action of Ta. Table 5 shows that in both types of patch of $Mo^{dp}+/+Ta$ females the proportion of zigzag hairs was intermediate, i.e. Ta was acting partially in both.

Table 5. *Hair counts from offspring of crosses involving tabby and dappled*

Genotype	No. of mice	Sample region	No. of hairs				% zigzag hairs
			Zigzag	Awl	Auchene	Guard hair	
$Ta+$	6	Stripe	35	283	14	—	10·5
		Normal	233	136	16	2	60·2
$Mo^{dp}+$	2	White	96	33	13	—	67·6
		Pigmented	99	30	5	1	73·3
$Mo^{dp}+/+Ta$	7	White	178	329	6	1	34·6
		Pigmented	127	328	3	2	27·6

(iv) *Crosses to obtain double heterozygotes in coupling*

(a) Dappled and Cattanach's translocation

The repulsion heterozygotes, $Mo^{dp}+/+fd$, carrying pp or cc^{ch}, obtained in the first stage of the experiment were crossed with pp, cc or $c^{ch}c^{ch}$ males. These matings had three functions; they tested the genotype of the presumed heterozygotes, provided data on the frequency of recombination between Mo^{dp} and the translocation break, and, if recombination occurred, would provide coupling heterozygotes, $Mo^{dp}fd/++$, for further test of the inactive-X theory.

In the absence of crossing-over all offspring were expected to carry either Mo^{dp} or the translocation (Table 6). Crossover animals would carry both or neither. Table 7 shows that out of ninety offspring obtained so far in crosses using pp all have been of the non-crossover type. This result has amply confirmed the genotype of the $Mo^{dp}+/+fd$ mothers, but leaves the phenotype of $Mo^{dp}fd/++$ females still in doubt. In the crosses with c^{ch} the $Mo^{dp}fd/++$ type was not expected to be distinguishable from $Mo^{dp}+$, but no other crossovers were found.

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Table 6. *Expected phenotypes of offspring from a linkage test of type* $Mo^{dp}+/+fd\,pp♀ \times ++pp♂$

	Female			Male	
	Phenotype			Genotype	Phenotype
Genotype	Coat	Eyes			
NON-CROSSOVERS					
$Mo^{dp}+/++$	White/pink-eye	Pink		$Mo^{dp}+$	Dies
$+fd/++$	Wild/pink-eye	Dark		$+fd$	Wild-type
CROSSOVERS					
$Mo^{dp}fd/++$	White/pink-eye	Dark		$Mo^{dp}fd$	Dies
$++/++$	Pink-eye	Pink		$++$	Pink-eye

Table 7. *Offspring of crosses to obtain coupling heterozygotes for dappled and Cattanach's translocation*

	Offspring						
	Female				Male		
Parents	$Mo^{dp}+$	$Mo^{dp}fd$	$++$	$+fd$	$++$	$+fd$	Total
$Mo^{dp}+/+fd\ pp♀ \times ++\ pp♂$	14	—	—	37	—	39	90
$Mo^{dp}+/+fd\ cc^{ch}♀ \times ++\ c^{ch}c^{ch}$ or $cc♂$	10		—	13	—	6	29

(*b*) *Tabby and striated*

Females judged from the appearance of their coat to be of the genotype $Str+/+Ta$ were mated to normal wild-type males. The male offspring were scored as tabby or wild-type and discarded, thus providing data on recombination between tabby and striated. The female offspring could be classified as striped or not, by inspection. Those striped animals in which short patches could be found by stroking the fur backwards were then classified as carrying *Str*, and the remainder as being $Ta+$ heterozygotes, not carrying *Str*. At six weeks old or later hair samples from all the *Str*-carrying animals were examined in order to test whether these animals also carried *Ta*. A single $Ta+$ animal from each litter was examined also, as a control.

Twelve presumed $Str+/+Ta$ females were mated and the genotypes of all were confirmed. Table 3 shows the results obtained from the studies of hair samples from offspring of these crosses. The two animals classified as $TaStr/++$ were suspected of carrying *Ta* before hair samples were taken from them, since they had the slightly reduced eye aperture which all tabby males and some $Ta+$ females have. Their hair samples showed clearly that the gene *Ta* was acting in the short patches of their fur, where *Str* was acting. As expected on the inactive-X theory, there was no sign of the action of *Ta* in the normal length patches. No other *Str*-carrying females had the reduced eye aperture of $Ta+$ animals, and none showed any sign of the action of *Ta*.

There is the question whether all the *TaStr*/+ + animals showed the effect seen in these two or whether some were missed. Some idea of the expected number of *TaStr*/+ + can be obtained from the recombination fraction (Table 8).

The observation of sixty-one tabby to seven normal gives a recombination fraction in the male offspring of $10{\cdot}3 \pm 3{\cdot}7\%$. A similar result would be expected among the female offspring. The observed two *TaStr*/+ + and five normals out of eighty-five young give a recombination of 8·2%, which although lower than the result from the male offspring is not significantly so. Thus, there is no reason to think that some *TaStr*/+ + animals had been missed.

Table 8. *Results of linkage tests using* Str+/+Ta *heterozygotes*

	Offspring					
	Female				Male*	
Parents	*StrTa*	*Str*+	+*Ta*	++	*Ta*	+
Str+/+*Ta*♀ × + +♂	2	44	34	5	61	7
Recombination		7/85 = 8·2%			7/68 = 10·3%	

* Males carrying *Str* die *in utero*.

2. DISCUSSION

The inactive-X theory requires that in a heterozygous female each gene shall act fully in some patches of the body and not act in other patches, and this is what the experiments described here were designed to test.

In the tests with dappled and Cattanach's translocation the phenotype of the repulsion heterozygotes, Mo^{dp}+/+*fd*, showed that there were no spots in which neither gene was acting. It did not rule out the possibility that there were spots with both genes acting, since the colour produced would have been indistinguishable from that of dappled alone (Table 1). It would have been valuable to have had the complementary type of heterozygote Mo^{dp}*fd*/+ +, but this type was not found. There are two possible explanations for this: either animals of this type did occur but were not recognized because their phenotype was not as expected, or these animals did not occur because the frequency of recombination between Mo^{dp} and the translocation was very low. The second explanation seems much the more probable, firstly because no crossover animals of any other type were found, and secondly because Cattanach (1962) showed that the position of the translocation break in the X chromosome was such that it gave about 4% recombination with *Ta* on the side away from *Bn*. This means that it must be very close to Mo^{dp}, which also lies about four map units from *Ta* on the side away from *Bn* (Phillips 1961).

There still remains the possibility that when the coupling heterozygote is found it will show deviations from the expected phenotype, particularly in the crosses using pink-eye. The reason for this doubt is that in heterozygotes for Cattanach's translocation showing flecking for pink-eye the patches of *pp* colour occupy less than the expected 50% of the coat. There are various possible explanations for this.

Although the two cell types with normal and mutant genes active are expected to be equal in numbers in early embryology they might differ numerically in the adult through different rates of multiplication. Or the gene product of the pink-eye gene might be slightly diffusible so that normal pigment could be formed in cells genetically *pp* by diffusion in of the wild-type substance from neighbouring cells. Skin-grafting has shown that in adults either melanophores or some pigment precursor substance can diffuse across the edges of a graft (Silvers, 1961). A similar diffusion at an embryonic stage would produce a relatively greater effect in the adult coat. Cattanach observed a 'spreading effect' in translocation heterozygotes which were flecked for both *p* and c^{ch}, i.e. patches of pc^{ch} colour were surrounded by fringes of colour looking c^{ch} but not *p*. This could be explained by diffusion of the gene product of the wild-type allele of *p*. A similar 'spreading effect' might lead to fringes of wild-type colour around the dappled patches of a $Mo^{dp}fd/+\,+$ heterozygote carrying *pp*. Therefore the occurrence of wild-type hairs on such an animal would not invalidate the theory.

In the crosses with tabby and striated one can theoretically detect all four possible combinations of gene action. The only difficulty is that detection of the action of *Ta* is based on statistical measurement of hair types whereas recognition of individual hairs as affected or not would have been better. In *Ta*+ heterozygotes the hair counts indicated some overlap of effect of the two X chromosomes in the two types of patches: there were a small number of zigzag hairs in the abnormal patches and somewhat fewer zigzags than normal in the wild-type patches. This presumably indicates that the gene action of *Ta* is not entirely a localized one, and in any case means that the same overlap of effect should be expected in *Str*+/+*Ta* heterozygotes. Also, in *Str*+ females, the short patches of fur on the average cover less than half the body. As in animals flecked for *pp*, this could be due to diffusion of gene product, which again could lead to overlap of effect in *Str*+/+*Ta* heterozygotes. In view of these points the results obtained with *Str*+/+*Ta*, indicating no action of *Ta* where *Str* was acting, but some overlap in the non-*Str* patches, seem in good agreement with the theory. In *StrTa*/+ + the converse picture was very clearly obtained, thus removing the possibility that the failure of the two genes to act together in *Str*+/+*Ta* could be due to some epistatic effect of one or other gene. It is their relative chromosomal position which determines whether the two genes act together or alternately.

This converse picture is itself interesting. It must be the first time in genetics that cis and trans heterozygotes for two completely non-allelic genes, ten units of recombination apart, have been shown to be phenotypically different.

3. SUMMARY

The inactive-X theory of dosage compensation postulates that in all somatic cells of adult female mammals one or other of the two X chromosomes is genetically inactive. This means that in a female heterozygous for two non-allelic genes acting through the same cells, and carried one on each X chromosome, one or other gene should act in all cells. Conversely, if the two genes are carried on the same X, then

both genes should act in some cells and neither gene in the remainder. This point has been tested by breeding experiments with mice, using pairs of genes affecting coat colour and coat texture. In female mice carrying the colour mutant dappled, Mo^{dp}, on one X and a translocation including the wild-type alleles of pink-eye, *p*, and albino, *c*, on the other, either Mo^{dp} or the translocation acted in all cells. With the genes tabby, *Ta* and striated, *Str*, affecting coat texture, in *Str* + / + *Ta* females tabby acted only in the non-*Str* patches, while in *StrTa*/ + + it acted only in the *Str* ones. Thus these experiments confirm that only one of the two X chromosomes is active in the somatic cells of female mammals.

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