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Zigzag: a genetic defect of the horizontal canals in the mouse

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

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The name 'zigzag' has been given to a genetic behaviour defect in the house mouse (*Mus musculus* L.) in which the animals walk in a zigzag path. It arose spontaneously in a non-inbred strain of mice. The genetic studies reported in this paper have shown that the zigzag character is not due to a simple single gene change, but the anatomical studies have shown that the inner-ear defect responsible for the behaviour defect is different from all others previously reported, and for that reason it has been thought worth while to describe zigzag.

GENETICS OF THE 'ZIGZAG' CONDITION

Breeding within the stock in which zigzag animals were first found resulted in the production of some zigzag and some normal young from matings of both normal by normal and zigzag by zigzag (Table 1). This ruled out the possibility of the zigzag condition being due to a single gene with good penetrance, whether dominant or recessive.

Table 1. *Results of matings in the original zigzag stock*

	Offspring		
Parents	Zigzag	Normal	% Zigzag
Normal × Normal	14	54	20·2
Zigzag × Normal	30	174	14·7
Zigzag × Zigzag	22	74	22·9

To find whether the character behaved primarily as a recessive or as a dominant, zigzag animals were outcrossed to various stocks. With two of the outcross stocks, C57BL and YX, a few zigzag animals were observed in the F_1 generation (Table 2),

Table 2. *Results of outcrosses of zigzag animals from the original zigzag stock to unrelated stocks*

		Offspring	
Outcross stock	No. of pairs	Zigzag	Normal
CBA	5	0	54
C57BL	8	20	106
A	3	0	26
YX	5	3	82

and with the other two stocks no zigzags were found. This showed either that the zigzag character was the result of the action of a single dominant gene with very low penetrance, or else that the inheritance was polygenic with some normal stocks having a higher level of zigzag polygenes than others. To test these possibilities a stock giving a high frequency of zigzag was built up by selection, and then the breeding behaviour of the zigzag and normal young from this stock was studied. If

Table 3. *Results of selection for increased frequency of zigzag young in matings of zigzag × zigzag*

Generation	No. of pairs	Offspring		
		Zigzag	Normal	% Zigzag
1	2	13	33	28·3
2	5	28	28	50·0
3	8	73	71	50·7
4	2	18	8	69·2
5	6	48	35	57·8
6	6	44	17	72·1
7	4	35	11	76·1

$\chi^2_{[1]} = 27{\cdot}6 \qquad P < 0{\cdot}001$

zigzag were due to a single dominant gene whose penetrance had been improved by the selection, then non-zigzags from the selected stock should not carry the gene and should not throw zigzag young. The method of selection was to keep young for breeding from those pairs in any generation which threw the highest proportion of zigzag young; brother-sister mating was avoided. Table 3 gives the results of the

Table 4. *Results of test matings of zigzag and normal young from the zigzag stock after selection for high frequency of zigzag*

Parents		No. of pairs	Offspring		
♀	♂		Zigzag	Normal	% Zigzag
Zigzag × Zigzag		10	173	62	73·6
Zigzag × Normal		5	48	20	71·1
Normal × Zigzag		5	43	17	
Normal × Normal		4	50	76	39·7

selection and Table 4 of the test-matings which followed it. A χ^2 method due to Holt (1948) with a computational simplification by Dr B. Woolf was used to test the statistical significance of the apparent progress made by selection. Let a be the generation of selection; let A_1 and A_2 be $S(a)$ for all zigzag and normal young respectively; and let n_1 and n_2 be the total numbers of zigzag and normal young. Then

$$\chi^2 = \frac{(n_2 A_1 - n_1 A_2)^2}{n_1 n_2 S(a-\bar{a})^2}.$$

Although the number of pairs used in the selection experiment was very low it is clear that significant progress was in fact made. The proportion of zigzags in the sixth and seventh generations is consistent with the zigzag character being due to

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a single dominant gene for which the parents were heterozygous. The results of the test-matings show, however, that there was little difference in breeding behaviour between the normal and zigzag animals from the selected stock. Matings of zigzag × normal threw as high a proportion of zigzag young as matings of zigzag × zigzag, which gave results like those of the last generations of selection. The proportion of zigzag young from matings of normal × normal was lower, but all four pairs threw some zigzag animals, i.e. there was no reason to suppose that there was a single gene for zigzag which some pairs did not carry. Thus, the hypothesis that the zigzag character is the result of the action of a single dominant gene with modifiers is not supported by these data. There remains the alternative explanation of polygenic inheritance. In an attempt to obtain some idea of the number of polygenes involved zigzag animals from the selected stock were outcrossed and the young then intercrossed to obtain an F_2. Only about 1 in 50 F_2 animals was affected

Table 5. *Results of the outcross and following intercross of animals from the selected stock*

	No. of pairs	Offspring	
		Zigzag	Total
Outcross	2	1	69
Intercross	8	8	443

(Table 5). This is consistent with the 1 in 64 expected if zigzag were due to the simultaneous homozygosis of three unlinked recessive genes, but obviously many other polygenic situations are possible.

THE BEHAVIOUR DEFECT OF ZIGZAG MICE

The most usual characteristic of the zigzag mice was a zigzag motion of the head in walking and a tendency to describe a complete circle now and then. There was no vertical head-shaking; the animals showed normal responses to change of position and a normal 'landing reaction', and their hearing was normal. The expression of the defect varied. The most severely affected animals circled repeatedly, but at the lower end of the scale the zigzag head motion was sometimes very slight with no circling, so that the defect graded into normal.

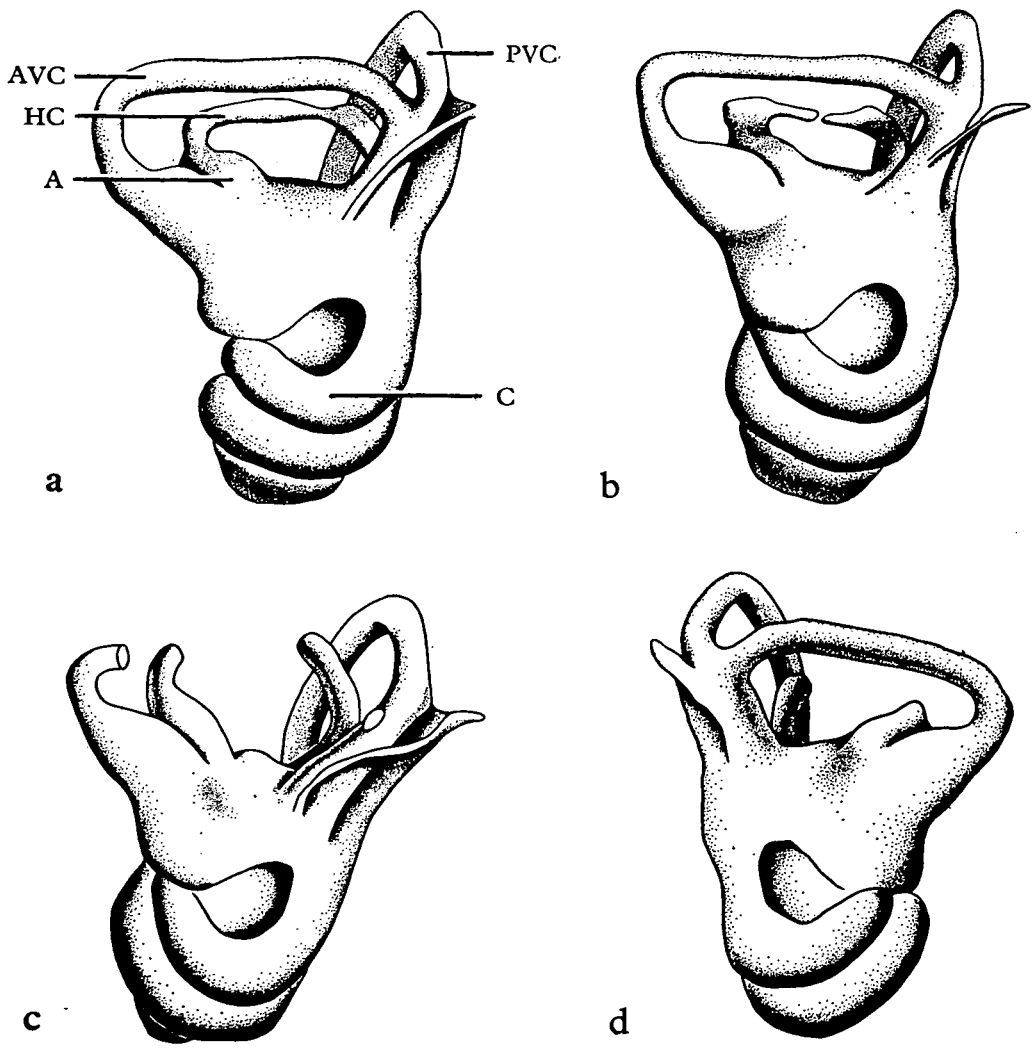
STUDIES OF THE INNER EAR DEFECT

Whole mounts of the bony labyrinth and sections of the inner ear were prepared by the methods of Lyon (1958).

The whole mounts showed that in zigzag animals there was either reduction or absence of one or both horizontal canals (Fig. 1). There were all grades of defect from complete absence of the canal to normality; in some animals one ear was normal and the other abnormal. Intermediate grades did not consist of shortening of the canal but of a constriction in the middle of its length. Sometimes this constriction was a simple narrowing, the narrow part varying in length from a mere

notch to about one-third of the canal length. Sometimes the middle portion of the canal was lacking, leaving blind-ending stumps at both ends. The stumps again varied in length according to the severity of the defect, but even in the most severe grades the ampulla of the canal was always present.

Sections of the inner ear revealed no additional abnormalities. The crista and ampulla of the horizontal canal were normal, as also was the remainder of the inner



Text-fig. 1. Camera lucida drawings of whole mounts of the bony labyrinths of zigzag mice, showing increasing grade of defect from a slight constriction of the horizontal canal in *a* to almost complete absence of the canal in *d*. *a*–*c* are from right ears and *d* is from a left ear. In *c* the anterior vertical canal has been cut away to give a better view of the horizontal canal. A = ampulla of the horizontal canal, AVC = anterior vertical canal, C = cochlea, HC = horizontal canal, PVC = posterior vertical canal.

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ear. The stumps of membranous canal ended blindly where the bony canal ended, or if the bony canal were merely constricted then a thin shred of tissue with no canal lumen passed through the constriction.

Of 22 zigzag animals examined, 18 had some abnormality of the horizontal canals of both ears and 4 had one ear normal and one abnormal. The ears of 11 apparently normal animals from the zigzag stock were also examined; 6 had both ears normal, 4 had one ear with some abnormality (merely a constriction in three cases), and 1 animal had both ears abnormal. Thus the correlation between ear defect and behaviour defect was good, but the one anomalous animal with abnormal ears and normal behaviour showed that the ear defects were not always incompatible with normal function of the ear.

COMPARISON WITH OTHER MUTANTS

Many mutants affecting the inner ear of the mouse are already known (Grüneberg, 1956) and they can be broadly divided into those in which the ear is morphologically normal but there are degenerative nerve changes, and those involving morphological defects of the ear. Zigzag clearly belongs to the second group, the defects of some of which are tabulated in Table 6. Other mutants affecting chiefly the canals are

Table 6. *The defects of some mutants with morphological effects on the inner ear*

Ear Defect				Behaviour		
Otoliths	Horizontal canal	Vertical canals	Mutant	Position response	Horizontal movement	Vertical movement
A	N	N	Pallid	A	N	N
N	A	N	Zigzag	N	A	N
N	A	A	Fidget	N	A	N
N or A	A	N or A	Twirler	N or A	A	N or A
N or A	A	A	Dreher	N or A	A	A
A	A	A	Kreisler	A	A	A

A = abnormal, N = normal

fidget and twirler. In fidgets all the canals are rudimentary (Truslove, 1956), and in twirlers the horizontal canals are chiefly affected but they are shortened rather than constricted as in zigzags, and the ampullae are abnormal (Lyon, 1958).

In fact zigzag is the only genetic ear defect of the mouse so far described in which the canals are constricted rather than shortened. There is thus no reason to suspect that zigzag might be a recurrence of a previously known mutant, and no high probability of it being allelic with any. No direct tests of allelism have been made, but the results of linkage tests suggest that no zigzag factor is allelic with kreisler, pallid or fidget. All three of these genes lie in linkage group V, as also does the agouti locus. Some matings in the zigzag stock could have given evidence of linkage of a zigzag factor with agouti or with pallid; no evidence of such linkage was found (Table 7). Thus there is no reason to suppose that any zigzag factor lies in this

Table 7. *Linkage tests between zigzag and two markers in linkage group V*

	Zigzag offspring			
	Observed		Expected*	
Parents	+	a	+	a
+ +/zga × + + /zga	6	2	6	2
+ +/zga × zga/zga	4	8	6	6
zg+/+a × zga/zga	2	6	4	4
	+	pa	+	pa
+ +/zgpa × + + /zgpa	5	1	4·5	1·5

* On the hypothesis of independent segregation.

linkage group. (All these matings happened to be ones which threw only a low proportion of zigzag young and therefore the linkage tests have been made simply by noting whether the segregation of agouti or pallid among the zigzag animals departed from that expected on the basis of independent segregation. The non-zigzag animals would yield very little linkage information as, on the hypothesis being tested, they must include a large proportion of the genetically zigzag animals as well as the true non-zigzags.) Tests with dreher and twirler have not been made.

DISCUSSION

The zigzag character does not show simple Mendelian inheritance. In this it resembles various other characters of the mouse, including hare-lip (Reed, 1936), duplicate incisors (Danforth, 1958) and white spotting (Dunn & Charles, 1937). The first question to be asked about such a character is whether it is determined by one major gene with modifiers or by several genes with equal effect. Wright (1934*a*, *b*), dealing with polydactyly in guinea-pigs, showed that the hypothesis of a major gene needs stringent test before it can be accepted. In the case of zigzag, simple breeding tests of normal and zigzag animals from the same stock showed no major genetic differences between them, and the results of outcrossing and intercrossing gave no indication of the segregation of a gene which could be described as 'major'. Thus zigzag is thought to be due to the action of genes which individually have only small effects. On crossing to different stocks, there were in some cases affected animals in the first generation and in some cases none. This suggests that the underlying developmental basis of the zigzag condition has a continuous distribution, the affected animals are those in which a certain threshold is passed, and the stocks concerned are genetically at different levels with respect to the threshold. The rapid progress which was made in the small selection experiment might appear to suggest that only a small number of genes were concerned, but this experiment started from a stock in which the level of the underlying basis must have been near the threshold for zigzag, since there were 28% affected animals in it. A different foundation stock might have resulted in very different progress. The hypothesis of a continuous underlying basis with a threshold for abnormality was first put forward

by Wright (1934*b*) to explain the inheritance of polydactyly in guinea-pigs and has since been suggested for various mouse characters, including absence of third molars (Grüneberg, 1951). It may thus be a common type of inheritance in mammals.

SUMMARY

The name zigzag has been given to an inherited behaviour defect in the mouse in which the animals walk with a zigzag motion. It is inherited polygenically. The anatomical defect responsible for the abnormal behaviour was a reduction or absence of the horizontal canals of the inner ear, the reduction consisting of a constriction in the middle of the canal length, rather than a shortening of the canal.

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