TWO NEW MUTANTS, 'TREMBLER' AND 'REELER', WITH NEUROLOGICAL ACTIONS IN THE HOUSE MOUSE (*MUS MUSCULUS* L.)

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(With One Text-figure)

I. Trembler (symbol *Tr*)

A dominant gene producing spastic paralysis, with convulsions in the young, and generalized tremor in the adult.

Origin

The gene described here under the name of 'Trembler' (symbol *Tr*) arose by spontaneous mutation in the autumn of 1946 in a stock maintained by Dr C. Auerbach at the Institute of Animal Genetics, Edinburgh. Abnormal young mice were first noticed by the animal attendant, and two of these with their parents were given to the present writer for investigation. None of the ancestors of these mice had been treated with mutagenic agents. The parents of the first Tremblers were themselves normal. They produced nine young of which four were Tremblers, and it was supposed that a recessive gene was responsible. This supposition, which nearly led to the loss of the gene, was soon proved to be wrong because the Trembler offspring when outcrossed to unrelated normal mice regularly produced about 50 % of Tremblers among their progeny, and the normal offspring of Tremblers when intercrossed produced no Trembler among twenty young.

Since the Trembler gene, as will be shown in detail below, seldom if ever fails to manifest in heterozygotes, it is probable that neither of the original parents was genetically a Trembler heterozygote, but that the original mutation occurred in the germplasm of one or other of them and so gave rise to a mosaic gonad. It is even possible that all the tissue of the gonad was heterozygous for the gene. The occurrence of mutations in this way appears to be not infrequent in mice. Cases reported in the literature include mutations from + to *Va* (Cloudman & Bunker, 1945), from *a* to A^{IV} (Little & Hummel, 1947), and from + to *c* (Dunn, 1934).

Description

The symptoms shown by Trembler heterozygotes appear first when the eyes have opened and the young mice become active. There is much variation in the age of onset and in the severity of the symptoms; some Tremblers can be detected at 12 days of age, but classification cannot be made with certainty till 18 days. When the juvenile symptoms are fully developed there is never any difficulty in recognizing the Tremblers. The symptoms characteristic of young Tremblers are paralysis, which is always present, and convulsions, which occur only on stimulation. The paralysis affects both pairs of legs and is spastic in type; there is hyperextension, particularly of the distal joints, and the legs in consequence

look stiff. Walking is achieved only with difficulty, the animal appearing to totter along on the tips of its toes. The paralysis is usually more conspicuous in the hind legs, which are often held out stiffly behind or to the sides. Stimuli, such as disturbance, picking up or transference to a different cage, aggravate the paralysis and induce convulsions. In a typical convulsion the spine is arched in dorsiflexion with the head bent downward. This position, which is illustrated in Fig. 1, is maintained for only a few seconds, and the spasm is followed by rhythmic contractions. First the head is bent back with the mouth open,

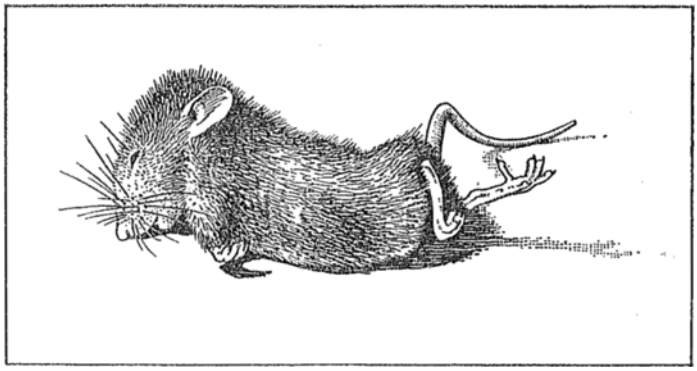


Fig. 1. Trembler heterozygote, 26 days old, showing typical posture during a convulsion. Drawn by Mr E. D. Roberts from a photograph.

and the head and neck undergo rhythmic vertical movements. The front legs are then rubbed against each other and against the face, an action that has the appearance of a fly cleaning its head and front legs. Sometimes the front legs beat violently up and down and the body rolls from side to side. These movements become more violent, then subside, and the convulsion is over. There is no relaxation and little appearance of exhaustion after the convulsion, and, though the paralysis remains, the mouse is generally able to move about until further excitement precipitates the next convulsion. Recurrent convulsions may be continued for several minutes without apparent injury to the mouse, and when the stimulus is prolonged the convulsions become temporarily less easily induced. These juvenile symptoms are characteristic of young Tremblers at about 3 weeks of age, but the severity of the symptoms and duration of the juvenile phase are very variable. In some the convulsions start at about 2 weeks and continue till 5 weeks; in others the phase lasts only for a few days.

Sometime towards the end of the juvenile phase the trembling that is characteristic of the adults begins to appear. It is more evident in the young that exhibit less violent convulsions, but the severity of the trembling in the adult has no obvious relation to the severity of the juvenile symptoms. The trembling consists of a very rapid side to side movement of the head and neck. The movement is so rapid that it can scarcely be followed by the eye, and it is quite different from the head movements associated with the waltzer-shaker type of syndrome. The trembling ceases when the animal is at rest. Convulsions are not normally observed in adults, but they can be induced by a strong stimulus such as clipping the ear, which is sometimes done for identification. The paralysis, on the other hand, invariably persists into adult life, but it is noticeably less severe than in the young, and the control of the limbs continues to improve throughout life, some elderly animals having a walking gait that is almost normal.

The growth of Trembler heterozygotes is retarded to an extent related to the severity of the juvenile symptoms. Tremblers at 3 weeks of age are noticeably smaller than their normal litter-mates, and the majority die soon after this age unless special precautions are taken. The cause of death is probably the animal's inability to obtain its food from the standard food-container and water from the drinking spout. Young Tremblers are accordingly given moist food in a small dish from the age of about 18 days until they have attained a reasonable size. It has been found desirable also to prevent the mother's impregnation at the post-partum oestrus in order to allow her to nurse the young beyond the normal weaning age of 3 weeks. With these precautions the mortality of young Tremblers is much reduced, and after the critical stage has been passed and the juvenile symptoms have disappeared, Tremblers grow well and attain a size little if anything below that of normal mice.

Trembler females breed normally, though the retardation of growth delays their maturity. Litters are of normal size and lactation is unimpaired. Trembler males, on the other hand, are frequently sterile, and those that breed do so irregularly. Out of fourteen Trembler males put with normal females only five were found to be fertile. These fourteen males were, moreover, selected for their healthy appearance and the mildness of their symptoms, so the actual sterility rate is probably much higher than these figures seem to indicate. It seems probable that the sterility is due to the physical difficulty of copulation caused by the paralysis of the hind legs.

Observation of the behaviour of Tremblers, both male and female, gives no cause to suppose that any mental defect is associated with the condition. Mothers, for example, bestow all the usual care on their young, and both sexes show the normal aggressive behaviour toward strange mice. This absence of mental defect is in striking contrast with the mutant described in the second part of this paper.

The senses also appear to be normal, at least so far as can be judged by ordinary observation. The pathology of Tremblers has not yet been investigated in any detail. A superficial examination disclosed no abnormalities in the external appearance of the brain. A preliminary examination of some sections of the brain was made by Dr G. J. Romanes, Department of Anatomy, Edinburgh University, and no gross abnormalities such as cavitation were found.

Segregation

The segregation data obtained from different types of mating of Tremblers are summarized in Table 1. The number of Tremblers in the progeny of normal females mated to Trembler males is in close agreement with the expectation of 50%. The progeny of Trembler females mated to normal males, however, show a slight deficiency of Tremblers, which is significant at the 2% level. The possible causes of this deficiency are discussed below. The intercross matings—Trembler by Trembler—were made in order to determine

Table 1. *Segregation data of Trembler*

Type of mating	No. of matings	Progeny			Deviation		Heterogeneity		
		Tr	+	Total	$\chi^2_{[1]}$	*P*	χ^2	D.F.	*P*
+ +♀ × *Tr* +♂	8	54	48	102	0·35	0·6	7·71	7	0·4
Tr +♀ × + +♂	25	217	272	489	6·19	0·02	24·74	24	0·5
Tr +♀ × *Tr* +♂	6	42	13	55	0·05	0·8	6·55	5	0·3

the phenotype of Trembler homozygotes. Careful examination of the young from these matings disclosed no differences in the form or severity of the symptoms that could be attributed to the presence of homozygotes; the gene was therefore either fully dominant, or lethal in the homozygote. Genetic tests of nine Trembler offspring of the intercrosses were made, and four were proved to be homozygotes; when mated to normal males they produced no normal offspring out of totals of 19, 18, 17 and 17 respectively. Homozygotes were thus proved to be viable and fertile. The segregation in the offspring of the intercrosses is in agreement, the ratio being close to the expected 3 : 1, though the numbers are not large enough to disprove a 2 : 1 segregation. The complete dominance of Trembler was unexpected because the majority of genes with heterozygous expression in mammals are incompletely dominant or lethal in homozygotes. Of the twelve previously known genes in the mouse that are classed as 'dominants' only two, Rex and Caracul, are fully dominant. Full, or complete, dominance is intended here only to mean that homozygotes and heterozygotes cannot be distinguished by ordinary observation of individuals' phenotypes. It is possible that more detailed observations of Trembler, as of Rex and Caracul, would reveal a difference in the average expression of heterozygotes and homozygotes.

The deficiency of Tremblers in the progeny of Trembler females may now be examined. It should first be pointed out that the deficiency is not necessarily confined to the offspring of Trembler females, because the heterogeneity in the ratios given by the reciprocal crosses is not very great [$\chi^2_{[1]}=2{\cdot}49$; $P=0{\cdot}1$–$0{\cdot}2$]. If the deficiency be accepted as real and not attributed to chance at sampling, two possible causes must be considered. These are misclassification due to incomplete penetrance or variable expression, and reduced viability before classification. Misclassification can be ruled out for the following reasons. In the first place there was no indication of incomplete penetrance in the offspring of the homozygous Trembler females. The results of the tests for homozygosity divided the animals tested sharply into two classes—those that gave approximately equal numbers of Tremblers and normals and were thus clearly heterozygotes, and those that gave only Tremblers and were thus homozygotes. There were four homozygous females which, when mated to normal males, produced a total of seventy-one offspring, all of which were phenotypically Trembler. If the penetrance in heterozygotes were 89% (the figure indicated by the pooled data from matings of heterozygous females), then the probability of finding no phenotypically normal animals among seventy-one known heterozygotes is only 0·0002. It is clear, therefore, that the penetrance in the offspring of these four homozygous females was complete. In the second place the variation of expression observed in Trembler heterozygotes gave no grounds for suspecting that any might be erroneously classified as normal. No difficulty was ever experienced in deciding whether a mouse was a Trembler or not, the distinction usually being perfectly clear-cut at, or before, 3 weeks of age; on the few occasions when the juvenile symptoms were not strongly developed, classification was deferred until the trembling appeared and the distinction became obvious. All the evidence, therefore, points to Trembler being fully penetrant in heterozygotes, and misclassification finds no support as a possible cause of the observed deficiency of Tremblers.

Reduced viability of Tremblers seems to offer a more likely explanation of the deficiency, though the evidence about it is inconclusive. Division of the litters of Trembler females into those that were intact at classification and those that had suffered one loss or more between birth and classification disclosed no significant difference in the ratio of Tremblers

to normals. (Litters were first examined between 0 and 3 days after birth.) The figures were as follows:

	Tr	+	*Tr* total
Depleted	77	82	0·48
Intact	140	190	0·42

$\chi^2_{(1)}$ heterogeneity = 1·5; $P = 0·2$.

At first sight this appears to contradict the hypothesis of differential mortality between birth and classification, since the deficiency would be expected to appear now entirely in the depleted litter class. But it was pointed out to the writer by Miss M. F. Lyon that if Tremblers die more frequently than normals then those litters that contain a larger number of Tremblers at birth will be the more likely to suffer loss. Therefore the division

Table 2. *Linkage tests with Trembler*

Gene tested (*x*)		Linkage group	Type of mating*	Phenotypes of progeny *Tr x*	*Tr* +	+ *x*	+ +	Total	Independence χ^2	Independence *P*	Recombination %	Recombination S.E.	Closest admissible linkage (%)
Sex	*Y*	—	b.c. ♂ C.	24	30	26	22	102	0·25	0·6	52	4·95	43
Non-agouti	*a*	V	b.c. ♀ R.	15	15	19	15	64	0·06	0·8	51	5·86	40
,,			mixed ♀ R.	3	7	3	13	26					
Brown	*b*	VIII	b.c. ♀ C.	8	13	12	8	41					
,,			b.c. ♂ R.	0	2	4	2	8	0·78	0·4	44	6·60	31
,,			mixed ♂ R.	4	10	2	9	25					
Albino	*c*	I	b.c. ♀ C.	4	2	9	7	22					
,,			b.c. ♂ R.	6	6	4	8	24	0·26	0·6	46	6·93	33
,,			mixed ♂ R.	2	10	0	6	18					
Pink-eye	*p*	I	b.c. ♀ C.	17	20	18	20	75	0·01	0·9	49	5·77	38
Dilute	*d*	II	b.c. ♀ C.	5	5	5	8	23	0·39	0·5	43	10·43	23
Piebald	*s*	III	b.c. ♀ C.	14	16	17	17	64	0·06	0·8	48	6·25	36
Waved-1	*wa*-1	XI	b.c. ♀ C.	18	24	23	20	85	0·95	0·3	45	5·42	34
Belted	*bt*	VI	b.c. ♀ C.	14	10	18	11	53	0·17	0·7	47	6·86	33
Caracul	*Ca*	VI	b.c. ♀ R.	12	8	16	8	44	0·36	0·5	55	7·54	39

* This column shows the type of mating—backcross or 'mixed', the sex of the segregating parent, and the phase—coupling or repulsion.

of litters into depleted and intact will be biased with respect to the Trembler ratio at birth, the depleted litters having the greater proportion of Tremblers. Thus the effect of differential mortality on the proportion of Tremblers is complex when the litters are divided into the depleted and the intact. The depleted litters will tend to contain more Tremblers at the beginning, but this initial excess will be more or less reduced by the subsequent death of some of the Tremblers. The intact litters, on the other hand, will tend to contain fewer Tremblers at the beginning, and this initial deficit will remain unchanged up to the time of classification. Therefore if there were differential mortality between birth and classification one would expect the depleted litters to show a smaller deficiency of Tremblers at classification than the intact litters; whereas if there were no differential mortality one would expect the two types of litter to show the deficiency equally. In fact the depleted litters did show a smaller deficiency than the intact litters, and the data give some support to the hypothesis of differential mortality. The difference is, however, not significant and the evidence is far from being conclusive. The total number of losses between birth and classification was only forty-one, and even if all of these had been Tremblers, which is most unlikely, they would not account for the whole deficiency of fifty-five. If, however,

there were also some mortality before birth the deficiency could well be attributed to reduced viability.

The apparent difference in the segregation ratios of the two sexes has some resemblance to the behaviour of Fused, a dominant gene of the mouse that produces kinks in the tail. There is a deficiency of Fused phenotypes among the progeny of all types of mating, but the deficiency is much greater when the female parent is Fused and the male normal than when the female is normal and the male Fused (Reed, 1937). The deficiency in this case is due to normal overlapping, the percentage of overlaps in Reed's data being fifty-one when the female parent was Fused and only twenty-one when the male parent was Fused. No explanation of this peculiar maternal effect has yet been found. (See discussion in Grüneberg, 1943, p. 193.)

Linkage Tests

Better mapping of the chromosomes and the addition of more marker genes are urgent needs in the formal genetics of the mouse. Though far from ideal, the Trembler gene would have some use as a marker, on account particularly of its dominance and the absence of mimic genes. Some tests for linkage have accordingly been made and others are in progress. The following loci were tested against Trembler, and no linkage was found: sex, non-agouti (*a*), brown (*b*), albino (*c*), pink-eye (*p*), dilute (*d*), recessive spotting (*s*), waved-1 (*wa*-1), belted (*bt*), Caracul (*Ca*). The data are summarized in Table 2. The majority of matings were double backcrosses, but a few were 'mixed', Trembler segregating as a backcross and the other locus as an intercross. The phase is stated as coupling when *Tr* and the dominant allele of the locus under test were derived from the same grandparent. Thus the crosses testing sex were of the type $Tr+Y/X\times+X/+X$: those testing, for example, pink-eye were $Tr+/+p\times+p/+p$: and those testing Caracul (in repulsion) were $Tr+/+Ca\times++/++$. The data were analysed by the method described by Mather (1935) and by Fisher (1946). The closest admissible linkage, at the 5% level of significance, shown in the last column of Table 2, was obtained by subtracting twice the standard error of the estimate from the observed recombination value. Some of the tests exclude the possibility of linkage closer than about 40%, and all exclude linkage closer than 30%, except that with dilute about which there is little information.

II. REELER (symbol *rl*)

A recessive gene that impairs the mechanism of balance.

Origin

This abnormality appeared in the spring of 1948 in the first litter of a brother-sister mating in a stock of 'snowy-bellied' mice (Eaton & Schwarz, 1946; Falconer, 1947), that was at least mildly inbred. An outcross had been made to another inbred strain, and after two backcrosses to the snowy-bellied stock the sib-mating was made that segregated the new mutant. Since both stocks were maintained by sib-matings and had not disclosed the mutant it is probable that the mutation was of recent occurrence. The segregation data, given below, prove the abnormality to be due to a single recessive gene. The name 'reeler', symbol *rl*, is suggested in default of a better, because it is superficially descriptive of the symptoms and does not presuppose any unproved pathological basis of the disorder.

Description

Reeler homozygotes can be recognized in a segregating litter when the young mice become active and run about; at about 15 days they are often smaller than their normal sibs and are less active, while at about 18 days classification can be made with certainty. The symptoms change little, and the following description applies to reelers of all ages. The most striking abnormality is the mouse's inability to keep its hindquarters upright. When the mouse stands still its hindquarters sway slowly from side to side; when it walks the swaying is accentuated and the mouse falls over on to its side. It rights itself immediately, but as soon as progression recommences it falls over again to the same or the opposite side. The whole performance is remarkably suggestive of inebriation, and strongly resembles the behaviour of normal mice when recovering from ether anaesthesia. Righting is, however, achieved easily and takes place as soon as the side of the body comes into contact with the ground. It is difficult to see exactly what happens when the mouse falls over, because the action is very quick. The falling seems to be due to the simultaneous adduction of one hind leg and abduction of the other. The mouse is not pushed over by a hyper-extension of the abducted leg because this leg is raised off the ground as the mouse falls over. Close observation usually discloses a slight tremor of the foot while it is off the ground. A more generalized tremor may sometimes be observed in a reeler that is excited and active. There is no tendency for a mouse to fall more often to one side than to the other; in fact, the tendency is rather for the direction of fall to alternate.

Reelers are less active than normal mice, and it is often difficult to induce them to run about so as to display their abnormality. When the cage is opened they are usually found crouching in a corner, often lying partially on their sides, which a normal mouse does not do, and they pay little attention to the disturbance caused by opening the cage. When induced to run about on a table they often fall off if they come to the edge, a thing that a normal mouse very seldom does. The fur of adults assumes an unkempt appearance which is probably due to lack of grooming, though reelers are well able to scratch with their hind legs. Neither males nor females show any sign of the normal aggressive behaviour toward strange mice. All these features suggest strongly that reelers are mentally deficient.

The physical symptoms improve slightly with age, and some old mice are able to run about without falling over; their gait is, however, far from normal, the legs being kept rather far apart, as if to give greater stability.

Little attempt has yet been made to find an anatomical basis of the abnormality. The normal posture of the head and front end of the body suggests that the labyrinth is normal. This conclusion is supported by the facts that reelers swim normally, adopt a normal posture when held up by the tail, and hear normally.

The growth of reeler homozygotes is retarded, probably by the difficulty of obtaining food and water, and many die at about 3 weeks of age. It has been found advisable, as with Tremblers, to delay weaning as long as possible and to provide moist food in a small dish. Males appear to be completely sterile; five males kept for a year with normal females failed to breed. The sterility of males may be due to the physical difficulty of copulation or more probably to the absence of normal sexual behaviour. The majority of females appear also to be sterile, probably for the same reasons, but one female has bred and another became pregnant but died before the birth of the young. The female that bred was not able to rear her young.

Segregation

The one reeler homozygote that bred was outcrossed to unrelated normal males and produced thirty-three offspring that survived to be classified; all were normal, and when mated *inter se* produced an F_2 consisting of 50 reelers and 176 normals. This ratio does not differ significantly from the expected 1 : 3, and the abnormality was thus proved to be due to a single recessive gene. Litters were examined twice a week, and reelers were classified as soon as they could be distinguished with certainty. There were, nevertheless, several deaths of undersized mice that were probably reelers but that could not be diagnosed with certainty. It seems probable therefore that the slight deficiency of reelers in the F_2—22·1% in place of 25%—though not statistically significant, was a real one. An additional ninety-seven F_2 mice were raised from two matings between mice known to be heterozygotes only from the occurrence of reelers in their progeny. These matings were the original one that produced the first reelers and a backcross of a normal daughter to this male. Of these ninety-seven mice, twenty-four were reelers. In the whole F_2 of 323 mice there were 22·9% reelers.

Linkage tests

Some data testing the linkage of reeler with five other loci was obtained from multiple intercrosses following the outcross of the fertile reeler female to an unrelated male that was homozygous for the genes non-agouti (*a*), brown (*b*), chinchilla (c^{ch}), dilute (*d*), short-ear (*se*) and belted (*bt*). The reeler female carried no other mutant gene except black-and-tan (a^t). Since dilute and short-ear are closely linked only five loci were tested. The classification of chinchilla in the presence of the other colour genes was found to be easy and certain if attention was concentrated on the small hairs on the inside of the ears. These are normally yellow even in non-agouti mice, but are pure white in chinchilla homozygotes, the distinction remaining clear in the presence of brown or dilute, or both. Three multiple intercross matings were made and 135 F_2 progeny were raised. The data, which are summarized in Table 3, show no significant deviation from independent segrega-

Table 3. *Linkage tests with reeler. All the tests were by the same three repulsion intercrosses, and the total number of offspring raised was* 135. *The estimates of recombination have all the same standard error of* 6·45%

Gene tested (x)		Linkage group	Phenotypes of progeny				Independence		Recombination (%)	Closest admissible linkage (%) ($P=0.05$)
			rl x	*rl* +	+ *x*	+ +	$\chi^2_{[1]}$	P		
Non-agouti	*a*	V	8	26	17	84	0·60	0·4	55	42
Brown	*b*	VIII	8	26	22	79	0·04	0·8	51	38
Chinchilla	c^{ch}	I	7	27	18	83	0·10	0·7	52	39
Dilute and short-ear	*d, se*	II	5	29	28	72	2·40	0·1	40	27
Belted	*bt*	VI	6	28	26	76	0·90	0·3	44	31

tion. The segregation with dilute and short-ear deviates in the direction that would be expected if there were linkage, but this deviation could well result from a reduced viability of short-eared reelers. Among the non-reelers was one long-cared dilute mouse representing a cross-over between *d* and *se*.

The linkage of reeler with sex was tested by seven matings between the offspring of the fertile reeler female and unrelated normal males. These matings were mixed crosses of the type *rl* $X/+X \times rl\ X/+Y$. A total of 226 offspring were raised, made up of

$$23\ rl\ ♀ : 27\ rl\ ♂ : 88 + ♀ : 88 + ♂,$$

and giving no suggestion of linkage. The estimate of the recombination between *rl* and sex is 53%, with a standard error of 5·76%, and the closest admissible linkage (at the 5% significance level) is therefore 41%.

Linkage tests are being continued as opportunity arises because a close linkage, if found, would simplify the maintenance of stocks of reelers.

Discussion

Much of the interest of a newly discovered mutant lies in the additional knowledge that it gives about the nature and variety of the genetical disturbances of structure or function that occur in the species. Before the discovery of Trembler and reeler, eleven different genes that regularly produce gross nervous abnormalities were known in the mouse. This group of mutants, which is reviewed and discussed by Grüneberg (1947), was remarkable for the similarity of the symptoms produced by so many different genes. All except one (jittery) included in its effects the familiar symptoms of the waltzing mouse, namely, circling movements, shaking of the head and usually deafness. The two new mutants are entirely different from these and from each other, and the variety of nervous disorders known in mice is thus much increased. The symptoms of Trembler, however, resemble in some respects those of jittery, described by DeOme (1945). Both exhibit spastic paralysis and convulsions in the young, and the form of the convulsions is similar though not identical in the two.

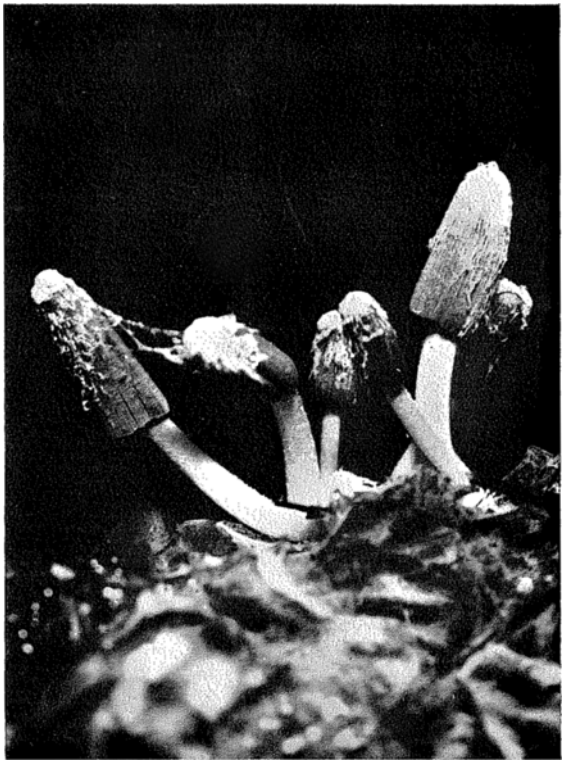
The mutants with neurological actions in other rodents have been reviewed by Grüneberg (1947). Some of these exhibit one or other of the features of Trembler. There is a recessive gene in rabbits that produces spastic paralysis of the hind legs; another produces a tremor and convulsions, but the paralysis which appears later in life is flaccid and not spastic. In *Peromyscus* there is a recessive gene that resembles Trembler more closely. It produces trembling and inco-ordination of movement; it is, however, invariably lethal. A recessive gene in guinea-pigs produces spastic paralysis of the hind legs with intention tremor and convulsions induced by stimulation.

Reeler appears to have no counterpart in other rodents. There is perhaps some resemblance to the symptoms of swayback, a disease of newborn lambs (Innes, 1939). The resemblance is, however, only superficial and swayback is not inherited.

The inherited nervous disorders of man are many (see Gates, 1946), and several of them appear to be comparable in some respects with Trembler. Since nothing is yet known of the pathology of Trembler or reeler—or, indeed, of most of the neurological mutants in mice—an attempt to make more detailed comparisons would be of little value. Until pathological investigations are undertaken on a larger scale we must be content to study only the more general genetic aspects of these mutants, and this study becomes more valuable as the number of mutants known in different species is increased.

Summary

1. Trembler (*Tr*) is a new dominant gene of the house mouse. It arose by spontaneous gonosomic mutation resulting in a mosaic gonad. It produces a spastic paralysis, more severe in the hind legs, and in the adult a generalized tremor that ceases when the animal is at rest. The young exhibit convulsions when stimulated. Viability is probably somewhat reduced, and this may have been the cause of a deficiency of Tremblers in the progeny of



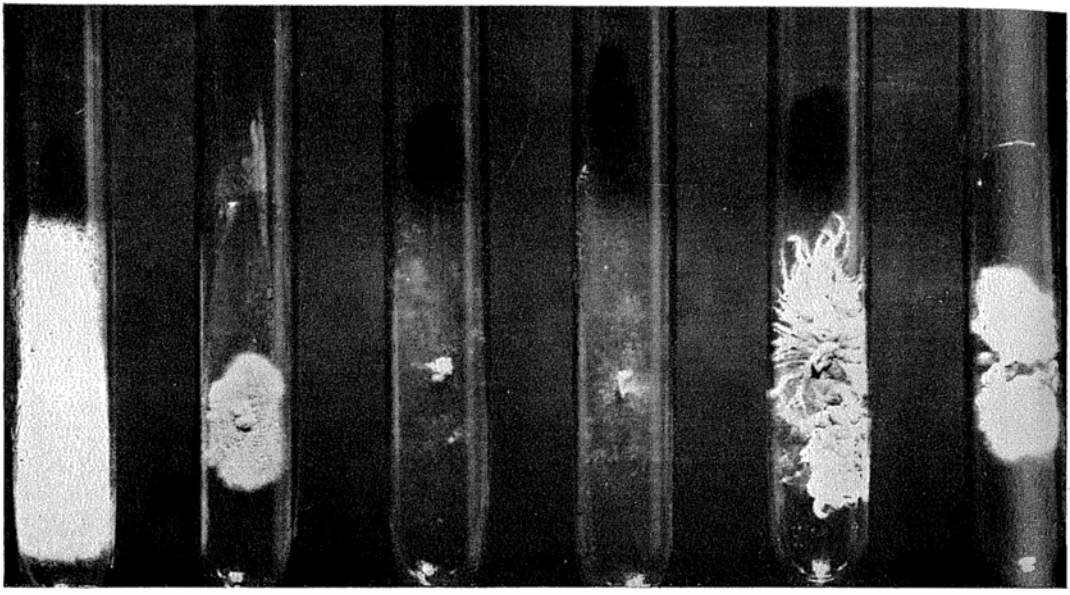


Fig. 1. Fig. 2. Fig. 3. Fig. 4. Fig. 5. Fig. 6.

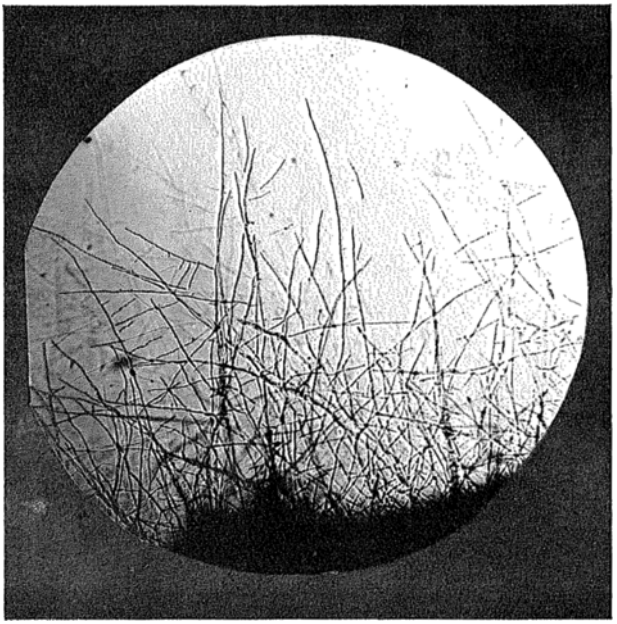


Fig. 1.

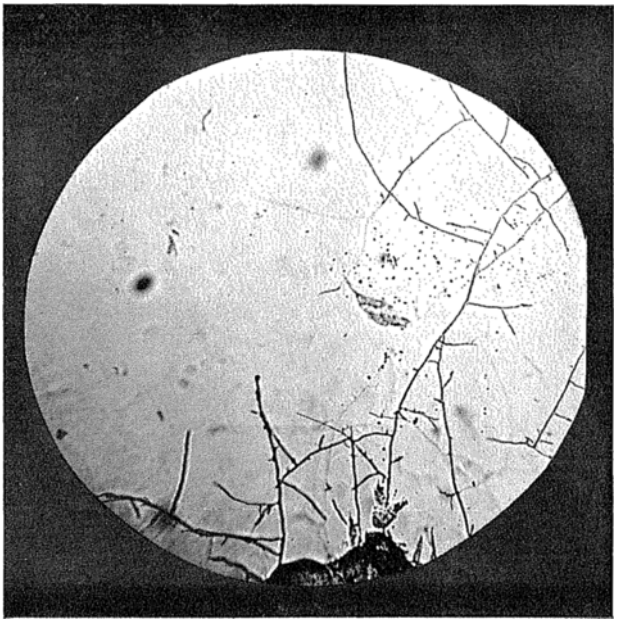


Fig. 2.

this is presumably not the case in *Coprinus*, where the two nuclei are maintained side by side owing to the system of synchronous division. Such a mycelium in *Coprinus* might perhaps be called a 'heterodikaryon', and it would seem that, as far as the dikaryotic phase is concerned, selection can only act between mycelia of this kind.

An attempt is being made at present to obtain a mycelium made up of two different mutants of the same or incompatible mating types. Since hyphal fusions, without formation of clamp connexions, occur readily between incompatible normal mycelia, it would seem possible that such a fusion could be obtained between two different mutant strains. If this were the case it would represent yet another type of heterokaryon, in which genetically different nuclei would presumably occur singly in the cells of the hyphae, and would not divide synchronously. In such a mycelium the individual cells would be subject to natural selection.

SUMMARY

The method used for the culturing of *Coprinus lagopus*, and for the production of X-ray mutants, has been described.

The mating type exhibited by this group has been outlined and the independent inheritance of the mating type genes has been shown.

Four morphological mutants have been described, one of which is linked with one of the mating type genes.

The action of natural selection with regard to the binucleate condition of the secondary mycelium has been discussed.

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REFERENCES

BEADLE, G. W. & COONRADT, V. L. (1944). Heterocaryosis in *Neurospora crassa*. *Genetics*, **29**, 290.

BENSAUDE, M. (1918). *Recherches sur le cycle évolutif et la sexualité chez les Basidiomycètes*. Pp. 1–156. Paris: Nemours.

BULLER, A. H. R. (1924). *Researches on fungi*, **3**. London: Longman, Green and Co.

BULLER, A. H. R. (1931). *Researches on fungi*, **4**. London: Longman, Green and Co.

FRIES, L. (1948). Mutations induced in *Coprinus fimetarius* (L.) by nitrogen mustard. *Nature, Lond.*, **162**, 846.

HANNA, W. F. (1924). The dry-needle method of making monosporous cultures of hymenomycetes and other fungi. *Ann. Bot., Lond.*, **38**, 791.

HANNA, W. F. (1925). The problem of sex in *Coprinus lagopus*. *Ann. Bot., Lond.*, **39**, 431.

EXPLANATION OF PLATES

PLATE 3. Fruit-bodies of *Coprinus lagopus*, growing on sterilized horse-dung.

PLATE 4. Mycelia growing on agar slants, 10 days old.

Fig. 1. Normal monokaryon, producing a plentiful aerial mycelium.
Fig. 2. Mutant **k**. The aerial mycelium is much reduced.
Fig. 3. Mutant **m**. The aerial mycelium is suppressed.
Fig. 4. Mutant **e**. The aerial mycelium is suppressed.
Fig. 5. Mutant **o**. The aerial mycelium is much reduced; the edge of the colony is filamentous.
Fig. 6. The dikaryon produced by the mutant mycelia **m** × **k**. The appearance of the colony is nearly normal.

PLATE 5. Hanging-drop cultures, 2 days after inoculation (× 150).

Fig. 1. Normal monokaryon.
Fig. 2. Mutant **m**.