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High frequency of a lethal gene (t^e) in a laboratory stock of mice

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1. INTRODUCTION

One locus affecting tail length in the house mouse is noted for its numerous mutant alleles, many of which are lethals. One allele, brachyury (T), is unique and all the others form a single group of tailless alleles jointly symbolized by t. Particular members of the group are referred to by adding superscripts as in t^0, t^{12}, t^{w11}, t^e. Homozygotes for some t alleles are viable, as also many heterozygous compounds of two different t-lethals. Homozygotes for T and for t-lethals die at various stages of embryonic development specific to each allele; Tt mice are tailless; $T+$ short-tailed; $+t$ and viable animals with two t's are normal-tailed. Although segregation from heterozygous females is quite normal, males that are heterozygous for almost any t-lethal transmit it to much more than half their offspring (Dunn, 1957; Dunn & Gluecksohn-Schoenheimer, 1950). This anomaly is clearly shown in test-matings to which the allele T is introduced so that the two types of spermatozoa leave distinguishable offspring. For example, when Tt fathers are paired with $++$ mothers, most offspring receive the father's t gene and are $+t$, while few are $T+$. Similarly, when spermatozoa of $+t$ fathers fertilize T eggs from $T+$ and Tt mothers, there are far more Tt than $T+$ offspring (products of the other eggs are disregarded here, being either indistinguishable from normal or inviable). Segregations in such test-matings have been used as direct measures of the frequency of t in effective spermatozoa. The excessive transmission of t-lethals by effective spermatozoa confers such powerful advantages on the genes that, in spite of their lethality, they often occur at high frequencies in natural populations (Dunn, Beasley & Tinker, 1958). Theoretically, there is no limit to the proportion of phenotypically normal individuals that could carry a particular lethal, and if t was transmitted by all effective spermatozoa from $+t$ males a stable situation would rapidly be reached where every living individual was heterozygous for t (Bruck, 1957). However, the proportion of $+t$ mice does not appear to be entirely determined by the frequency of t-bearing spermatozoa. Thus Dunn *et al.* (1958) reported fewer heterozygotes for t-lethals in fourteen feral populations than would be expected from the average frequency of t-lethals for effective spermatozoa in test-matings. This discrepancy was aggravated by finding that $+t$ males were more viable in the laboratory than homozygous normals.

It was precisely to avoid the uncertain validity of parameters estimated for feral

mice under laboratory conditions that the present work was undertaken with a laboratory stock. Yet even here, as will be seen later, the transmission of t by effective spermatozoa inadequately accounted for the $+t$ mice that this time were too numerous. Besides reporting this situation, the present paper examines the assumptions made in comparing actual and expected frequencies of $+t$ mice, namely: the laboratory stock segregated for only one t allele and this was fully lethal; stock $+t$ and $++$ mice were equally viable and fertile; in the test-matings used for assessing the frequency of t and $+$ spermatozoa, Tt and $T+$ offspring were equally viable, and the phenotypes of these offspring fully penetrant. As these assumptions are found valid it is concluded that the frequencies of t-bearing spermatozoa assessed for test-matings cannot legitimately be applied to stock matings. It is supposed that the segregation of t-lethals in effective spermatozoa is not purely a paternal characteristic but is also a property of the mother or her eggs.

2. MATERIAL

The present investigation makes use of two kinds of animals—'stock' and 'testers'. Stock animals are from the laboratory stock which segregated naturally for the t-lethal of this investigation; testers are hybrid animals made heterozygous for the allelomorph T.

The precise origin of the t-lethal is not known as the stock was based on a number of inbred lines and heterozygous populations. Breeding has since continued for thirty generations within a closed population, and for the last seventeen generations two sub-populations have been maintained. In the tables these are referred to as lines A and B. The investigations were made on the sixteenth and seventeenth generations following the separation. The lethal gene, which was first found by Dr A. W. H. Braden, occurs in both lines and has been named tailless-Edinburgh (t^e) (Bateman, 1957). To facilitate analysis of the genetic situation, stock animals were mated individually to testers of the constitution $T+$ or Tt^e. These were obtained from earlier crosses between stock animals (which supplied $+$ and t^e) and an unrelated strain that contributed T. A list of the genes and genotypes relevant to the investigation is given in Table 1.

Table 1. *List of genes and viable genotypes at the* t*-locus*

Symbol	Full name
	Genes
t^e	tailless-Edinburgh (lethal)
$+$	normal
T	brachyury (lethal)
	Viable genotypes
$++$	normal-tailed, homozygous normal
$+t^e$	normal-tailed, carrier
$T+$	short-tailed
Tt^e	tailless

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3. METHODS

Various experimental methods were employed details of which are perhaps best deferred. Here, it is intended to describe only the more general methods. Usually, mice from the laboratory stock, all of which looked normal, were mated to tester animals heterozygous for brachyury (T). Homozygotes would have been better, but the brachyury gene is unfortunately itself a lethal. The gametic unions of t^e with T and of $+$ with T resulted in tailless and short-tailed individuals. These unions were useful for distinguishing carriers from homozygous normals, and for estimating gametic ratios of $t^e : +$. In both cases, information was gained only from conjugations involving the testers' T gametes, and in this regard, Tt^e and $T+$ females were equally suitable. Tt^e males were not used in the tests because of the rarity with which they produced offspring by their T-bearing spermatozoa. No useful information could be gained from t^e and $+$ gametes uniting with similar gametes from the testers, as the surviving foetuses were all normal-tailed. These progeny of the test-matings were therefore disregarded. The progeny were classified on their day of birth when the three phenotypes could be distinguished without error.

4. RESULTS

Lethality of homozygotes

Not all genes that form tailless zygotes with the brachyury gene give lethal homozygotes, and the lethality of new tailless genes cannot be assumed. The viable combinations of tailless genes (either homozygotes for a viable, or heterozygotes for two different lethals) are normal-tailed. Homozygotes for brachyury die in early gestation. The usual test of the lethality of new genes is to mate tailless mice together, $Tt \times Tt$. If the t gene is a lethal, a balanced lethal stock is formed where TT and tt zygotes die *in utero* and only Tt heterozygotes survive; all the offspring are then tailless. But if the t gene is a viable, tt offspring survive and are recognized by their normal tails. Eight $Tt^e \times Tt^e$ matings were made between testers: all their sixty-six progeny were tailless, showing t^e to be a lethal gene.

It was felt necessary to ascertain that t^e was also lethal in the laboratory stock itself, and to ensure that no other tailless allele (t^x) segregated. For the excess of carriers discovered when tt mice were expected to die (see Interpretation) might well disappear if some tt mice (whether $t^e t^e$, $t^e t^x$ or $t^x t^x$) survived. Survival of tt males would in no way affect the situation because, being invariably sterile, their genotypes could not be tested nor could they contribute genes to subsequent generations. However, tt females are fertile, and they affect the results in two ways. Their number should be deducted from the apparent number of $+t$ mice, and the expectation of $+t$ should be increased on account of the additional number of t eggs tt females provide. The excess of carriers would disappear if about one-quarter of supposed $+t$ females were fertile tt females. Accordingly, a test of heterozygosity was made as follows. Stock females that had borne no short-tailed offspring from their test-matings, but were known to carry one t gene because they had produced tailless offspring, were re-mated to $T+$ tester males. Whereas $+t$ females could

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have both tailless and short-tailed offspring, *tt* females would have no short-tailed offspring. Eventually, out of one hundred females tested, ninety-nine proved to be $+t$; i.e. they had both tailless and short-tailed offspring. The remaining female provided no information on heterozygosity as she bore only a single tailless offspring. Tailless-Edinburgh is therefore established as the only *t* allele segregating in the stock and as a fully lethal gene.

Survival of normals and carriers

The genotypes were tested for forty-nine progeny from stock matings that, having been made between $+t^e$ ♀♀ × + + ♂♂, were expected to yield carriers and homozygous normals in equal numbers. Actually, 23 $+t^e$'s and 26 + +'s were observed, i.e. $0{\cdot}47 \pm 0{\cdot}07$ were $+t^e$'s. Most likely animals of these genotypes were equally viable up to the time of the test, and long after they would normally have weaned the next generation and have been discarded. Although the numbers were small, there was clearly no repeat of the situation reported by Dunn *et al.* (1958) for similar progenies of feral extraction for which the ratio was 35 : 18.

Fertility of carriers and normals

It was routine practice in managing the laboratory stock to leave the males and females together for 16 days after pairing, and to discard as 'failed' those parents that did not conceive within this period. In the second of the generations studied here both failed and successful parents were re-mated to $T+$ and Tt^e testers and eventually all but nine of the intended parents were tested. The incidence of carriers and normals is shown for each class in Table 2. There was no evidence that carriers and homozygous normals differed in fertility.

Table 2. *Indicence of carriers and homozygous normals among failed and successful parents.* (*Observations on males weighted by number of matings*)

Sex	Stock mating	Tested			Not tested
		Total	Carriers	Normals	
Dams	Failed	33	29	4	9
	Successful	91	71	20	0
	Total	124	100	24	
Sires	Failed	39	33	6	0
	Successful	94	71	23	0
	Total	133	104	29	
Sexes combined	Failed	72	62	10	9
	Successful	185	142	43	0
	Total	257	204	53	

Heterogeneity tests:

Source	D.F.	χ^2	P
Within sexes	2	2·83	0·25
Sexes combined	1	2·77	0·10
Dam-sire interaction	1	0·06	0·80

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Efficacy of the zygotic Tt^e : T+ *ratio as a measure of the gametic* t^e : + *ratio*

The ratio of t^e : + gametes for stock males was to be measured by the zygotic ratio of Tt^e : $T+$ in their test litters, and it was therefore necessary to find whether Tt^e and $T+$ embryos were equally viable. Information from the males' own test litters was scanty. The question was whether similar numbers of T eggs from tester females were represented by the birth of predominantly Tt^e litters sired by $+t^e$ males as in the entirely $T+$ litters (always disregarding normal-tailed offspring) of + + males. The comparison was confined to first litters. In view of the small number of + + males tested it was expedient to pool the information from successive generations, from A and B lines, and from Tt^e and $T+$ tester females. This procedure appeared valid as group means respecting $+t^e$ males were quite unform. A mean number of $3{\cdot}65 \pm 0{\cdot}22$ tailless and short-tailed offspring were born to $+t^e$ males, and $3{\cdot}50 \pm 0{\cdot}39$ short-tailed offspring to + + males. This evidence on differential mortality of Tt^e and $T+$ embryos is quite uncritical.

It was possible with the test litters born to a much larger number of $+t^e$ females to arrive at critical, if indirect, evidence on this matter. Because $+t^e$ females segregate normally it would be reasonable to expect their test litters to produce equal numbers of Tt^e and $T+$ offspring. Actually, a slight bias favouring Tt^e embryos was expected in the overall figures for the following reason. The litters were originally required to determine the genotypes of the tested parents, so no further litters were raised after the first diagnostic Tt^e young appeared. In consequence, test litters of $+t^e$ females that had only one young were 100% Tt^e, instead of the 50 : 50 Tt^e : $T+$ expected in an unbiased sample. Larger litters would be subject to bias of a lesser order. The bias was excluded by restricting the data to litters that contained both Tt^e and $T+$ offspring. The numbers of tailless and short-tailed offspring in this material were 94 : 97 for one generation and 162 : 157 for the other. In neither generation was there any evidence of differential viability of Tt^e and $T+$ embryos. Unless other mothers react violently to these embryos, it is to be concluded that their peculiar frequencies in the test litters of $+t^e$ stock males mirror the underlying ratio of t^e : + genes in the spermatozoa which were successful in fertilization.

Proportion of carriers

Individuals from two successive generations of the stock A and B lines were tested with $T+$ and Tt^e mates. Each individual was either diagnosed as a carrier by the appearance of tailless progeny, or was regarded as a homozygous normal if no tailless but four or more short-tailed progeny appeared. The average number of short-tailed progeny for individuals in this latter class was actually 6·5 and the probability of a carrier escaping recognition was thus usually considerably less than one-sixteenth. The frequency of carriers may therefore be slightly underestimated, but certainly not overestimated. Table 3 gives the numbers of carriers and normals for each of the four subdivisions of the stock. Since the results were homogeneous, although the two lines had been maintained separately for many generations, the proportion of carriers is understood to have reached a stable level in both lines. The figures show

that 80% of individuals were carriers, and this is taken to be their equilibrium frequency.

Table 3. *Numbers of carriers and homozygous normals in four subdivisions of the tested male and female breeding stock*

Line	Generation	Total tested	Carriers	Normals	Expectation
A	1st	50	36	14	40:10
	2nd	85	67	18	68:17
B	1st	43	38	5	34: 9
	2nd	86	70	16	69:17
	Total	264	211	53	211:53

Heterogeneity tests:

Source	D.F.	χ^2	P
Lines	1	2·27	0·14
Generations	1	0·01	0·91
Interaction	1	1·77	0·18
Overall	3	4·05	0·25

Overall frequency of carriers ($+t^e$) = 211/264 = 80%.

Percentage t^e *in effective spermatozoa from all stock males*

The proportion of t^e and + spermatozoa uniting with T eggs was determined for all stock males (carriers and normals) from the numbers of Tt^e and $T+$ progeny in their first litters from matings to Tt^e and $T+$ tester females (Table 4). The four subdivisions of the stock, provided by two lines in two generations, are shown to

Table 4. *Segregation of* Tt^e *and* T+ *progeny in the first test litters of stock males mated to* Tt^e *or* T+ *tester females. (Normal-tailed young excluded)*

		Progeny			
Line	Generation	Total	Tt^e	$T+$	Expectation
A	1st	87	60	27	62:25
	2nd	83	54	29	59:24
B	1st	72	54	18	51:21
	2nd	92	69	23	65:27
	Total	334	237	97	237:97

Heterogeneity tests:

Source	D.F.	χ^2	P
Lines	1	2·55	0·11
Generations	1	0·08	0·76
Interaction	1	0·50	0·48
Overall	3	3·13	0·40

Overall frequency with which t^e was transmitted by the effective spermatozoa of all stock males = 237/334 = 71%.

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have given homogeneous results and lead to the combined estimate that 71% of the entire sperm population fertilizing T eggs transmitted t^e. It would normally be presumed that t^e was transmitted in the same frequency by spermatozoa fertilizing other eggs.

Percentage of t^e *spermatozoa from* $+t^e$ *stock males*

The number of t^e and + genes among the effective spermatozoa of carriers only was estimated as the incidence of Tt^e and $T+$ progeny in the first test litters of stock males thereby (or subsequently) proven to be carriers. It can be seen from Table 5 that the four independent estimates of the ratio of t^e-bearing to +-bearing spermatozoa fertilizing T eggs are homogeneous, and that t^e entered 87% of those spermatozoa from carriers. Dunn's school refer to this ratio as the male segregation ratio advantage.

Table 5. *Segregation of* Tt^e *and* $T+$ *progeny in the first test litters of known carrier males in matings with* Tt^e *or* $T+$ *tester females. (Normal-tailed progeny excluded)*

		Progeny			
Line	Generation	Total	Tt^e	$T+$	Expectation
A	1st	71	60	11	62: 9
	2nd	61	54	7	53: 8
B	1st	61	54	7	53: 8
	2nd	78	69	9	68:10
	Total	271	237	34	237:34

Heterogeneity tests

Source	D.F.	χ^2	P
Lines	1	0·28	0·60
Generations	1	0·28	0·60
Interaction	1	0·35	0·55
Overall	3	0·91	0·80

Overall frequency of t^e in effective spermatozoa from stock $+t^e$ males = 237/271 = 87%.

The offspring of carrier males $(+t^e)$ *from stock matings with normal females* $(++)$

The genotypes were obtained for twenty-nine offspring from stock matings between normal females and carrier males and all proved to be carriers. If the estimate (based on conjugations with T eggs) that t^e entered 87% spermatozoa from $+t^e$ males applied equally to matings with normal stock females, some 3·2 normal progeny would be expected among the twenty-nine tested. The chance that no homozygous normals were found would be $0{\cdot}87^{29}$, or 0·02. It appears unlikely that the frequency of t^e spermatozoa was the same in test and stock matings.

5. INTERPRETATION

The proportion of carriers expected in any generation depends on the frequencies of t^e genes for uniting gametes, and may be found as follows. Let p be the proportion

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of carriers among the parents and P be the proportion of offspring of carrier males that receive t^e from their fathers. Then $\frac{1}{2}p$ eggs contributing to the next generation carry t^e and $1-\frac{1}{2}p$ carry +; whereas pP spermatozoa carry t^e and $1-pP$ carry +. Under random and non-assortative mating, $\frac{1}{2}p.pP$ gametic unions give lethal, $t^e t^e$, zygotes and only the remaining $1-\frac{1}{2}p.pP$ survive. The number of carriers

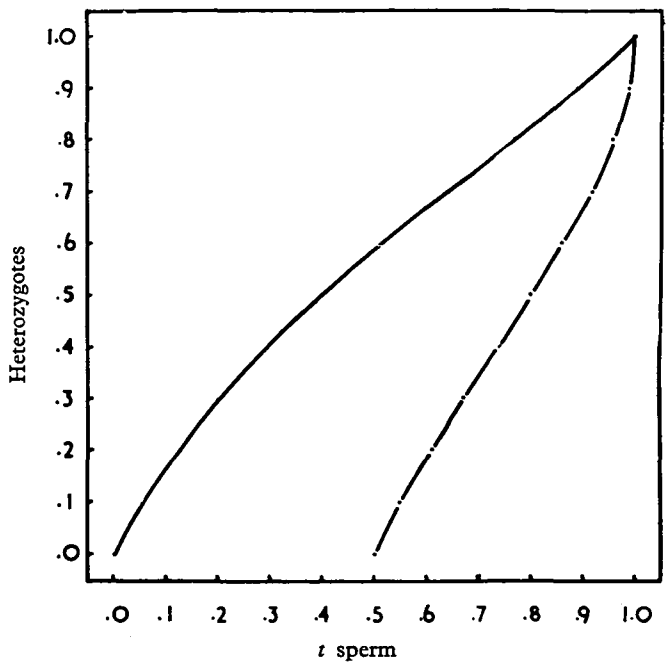

Fig. 1. Computed relationships at equilibrium between the incidence of heterozygotes and (*a*) the frequency of *t*-lethal sperm from the whole male population (continuous line) and (*b*) the segregation ratio of *t*-lethals in the sperm of heterozygous males (broken line).

among these is $\frac{1}{2}p.(1-pP)$ formed when t^e eggs are fertilized by + spermatozoa, together with $(1-\frac{1}{2}p).pP$ from + eggs fertilized by t^e spermatozoa. Thus, the proportion of carriers among the surviving offspring will be

$$p_1 = \frac{\frac{1}{2}p.(1-pP)+(1-\frac{1}{2}p).pP}{1-\frac{1}{2}p.pP}.$$

Eventually, p settles to an equilibrium value so that $p_1 = p$, reducing the above equation to $p = 1-\left(\frac{1}{P}-1\right)^{\frac{1}{2}}$. P then determines p. This relation was previously derived by Bruck (1957). (An incorrect relation provided by Prout (1953) arose through omitting the restriction that eggs could not be fertilized by eggs, nor spermatozoa by spermatozoa.) Where p is known, expected equilibria for pP and P can be found from the equations

$$pP = \frac{p}{1+(1-p)^2} \quad \text{and} \quad P = \frac{1}{1+(1-p)^2}.$$

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The continuous curve in Fig. 1 shows the relation of p to pP, and the broken curve relates p to P. It should be mentioned that about fifteen families per line constituted each generation of the stock. Inbreeding was minimized by pairing least-related individuals together. These departures from the model are not believed seriously to affect its applicability to the stock.

Observed values for the stock were

p = proportion of carriers = 0·80 (Table 3).
pP = proportion of offspring receiving t^e from their fathers = 0·71 (Table 4).
P = proportion of offspring of $+t^e$ males receiving t^e from their fathers = 0·87 (Table 5).

The evidence of Tables 3, 4 and 5 shows these figures represent equilibrium values as they are stable between successive generations and between lines with a distant common origin. The expected value of pP is $p \times P = 0{\cdot}70$; the agreement is so close that this compound parameter can be dropped from further consideration. However, P and p do not agree. Thus, the proportion of carriers expected from $P = 0{\cdot}87$ is $p = 0{\cdot}62$ (not 0·80), and conversely, $p = 0{\cdot}80$ gives the expected proportion of offspring from $+t^e$ males receiving their fathers' t^e genes as $P = 0{\cdot}96$ (not 0·87). It was nevertheless conceivable that the observations might yet be compatible with an intermediate value of P (and p). Dr E. C. R. Reeve, in an appendix to this paper, has developed the maximum likelihood solution appropriate to finding a single P that best fits both observations. His solution is $P = 0{\cdot}928$; $p = 0{\cdot}721$. Comparison of the data with these expectations (Table 6) yields $\chi^2_{(1)} = 19{\cdot}6$, Probability $\ll 0{\cdot}001$.

Table 6. *Contingency of observed* P *with observed* p *assessed against the maximum likelihood expectation that population* P = 0·928 *and the equivalent* p = 0·721

	Spermatozoa		
Estimate	Total	t^e	+
P	271	237 (251·49)	34 (19·51)
	Individuals		
	Total	$+t^e$	++
p	264	211 (190·34)	53 (73·66)
χ^2	(1 d.f.)	19·6	$P \ll 0{\cdot}001$

In fact, carriers are far more numerous than could reasonably be expected. What factor has been overlooked?

A clue to the situation lies in the observation in stock matings that twenty-nine carriers and no normals were found among the progeny of carrier males mated to normal females. Where P is the proportion of t^e spermatozoa from carriers, the probability that no normal spermatozoa leave offspring is P raised to the twenty-ninth power. The indirect estimate $P = 0{\cdot}96$ (based on the frequency of carriers in

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the stock as a whole) leads to a greater likelihood of finding only carriers in this particular section of the stock (Probability = 0·31) than the direct estimate $P = 0{\cdot}87$ obtained from the fertilization of brachyury eggs (Probability = 0·02).

It is inferred that segregations measured with the assistance of the brachyury gene are not strictly applicable to situations from which this gene is absent. If this conclusion is general, inconsistencies reported by Dunn, Beasley and Tinker may be similarly resolved. It is possible that the frequencies of the two classes of effective spermatozoa from *t* heterozygotes are specific to the genotypes of the eggs available for fertilization. Thus, if a female is heterozygous, say $T+$, the brachyury and normal eggs would return different ratios for the genes transmitted by the spermatozoa.

SUMMARY

A long-established laboratory stock was found to contain many individuals that were heterozygous for a lethal gene, called tailless-Edinburgh (t^e). Heterozygotes are indistinguishable from normals except by breeding tests with special tester stocks supplying brachyury (T) gametes, when tailless (Tt^e) progeny distinguish carrier parents from normal parents that produce only short-tailed ($T+$) progeny. When males are mated to tester females providing brachyury eggs, the ratio of $Tt^e : T+$ progeny reflects the ratio of $t^e : +$ spermatozoa. The proportion of t^e spermatozoa measured in this way led to the expectation that 62% of individuals in the original stock would be carriers, whereas 80% was found. Independent evidence is presented for $+t^e$ males that the incidence of t^e in their effective spermatozoa was higher when normal eggs were fertilized in matings within the original stock than when brachyury eggs were fertilized in outcross matings to the tester stock. These observations suggest that the proportion of t^e spermatozoa partaking in fertilization was modified by the genotypes of the females or of their eggs.

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NOTE ADDED IN PROOF

Recent information, not affecting the conclusions of the present paper, renders the account of the T-locus as given in the Introduction incorrect in two details.

Brachyury (T) is no longer unique: a second dominant allele named T-Harwell (T^h) has been described, only differing from the former in the age at which homozygotes die and in recombination frequencies when associated with some genes (Lyon, 1959).

And there are now three categories of mutant—(i) brachyury (T) alleles that shorten the tails of $T+$ heterozygotes; (ii) tailless (t) alleles that enhance the heterozygous effects of T and T^h; and the novelty (iii) a *suppressor* allele (t^{h7}, provisional symbol) which inhibits the heterozygous expression of T. Quite unlike Tt mice, Tt^{h7} mice are never tailless, have short tails only rarely, and usually have tails of normal length (Lyon, 1960).

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APPENDIX: ARE THE VALUES OF p AND P CONSISTENT WITH EQUILIBRIUM?

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We wish to test whether the observed values of p and P are consistent with the hypothesis that the population is in equilibrium such that

$$p = 1-\left(\frac{1}{P}-1\right)^{\frac{1}{2}} = 1-(Q/P)^{\frac{1}{2}}, \tag{1}$$

where $Q = 1-P$.

For this purpose, we shall calculate the maximum likelihood estimates of the two parameters, subject to the condition of equation (1), and test their agreement with the observed values of Table 3 (for p) and Table 5 (for P). The estimate of pP from Table 4 will not be used, since this largely duplicates the data of Table 5.

The likelihood equation from Tables 3 and 5 is

$$\log L = 211\log p + 53\log(1-p) + 237\log P + 34\log(1-P) \tag{2}$$

which contains only one independent variate, since p and P are related by equation (1). It may be maximized for P, using the relation derived from (1),

$$\frac{dp}{dP} = 1/2P\sqrt{(PQ)},$$

and, on putting $d(\log L)/dP = 0$, we obtain

$$\frac{211}{2P(\sqrt{(PQ)}-Q)} - \frac{53}{2PQ} + \frac{237}{P} - \frac{34}{1-P} = 0.$$

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This leads to the cubic equation in Q,

$$Q^3 - 1{\cdot}335{,}793Q^2 + 0{\cdot}435{,}773Q - 0{\cdot}024{,}920 = 0,$$

of which the roots are 0·86562, 0·39780 and 0·07236. The last of these yields our estimate of P:

$$P = 0{\cdot}9276,$$

whence

$$p = 0{\cdot}7207.$$

Using these two estimates in Tables 5 and 3, respectively, we can calculate the contribution to χ^2 of the deviation of observed from expected in each table, and the sum of the two values gives a χ^2 with one degree of freedom, since one has been lost in using equation (1). The result is shown below:

	Observed—Expected	Contribution to χ^2
Table 3 (p)	14·4	11·4
Table 5 (P)	20·7	8·1
	χ^2 for one D.F.	19·5

The deviation from expectation is highly significant, the observed P being too low and the observed p too high.

It should be noted that this test is not exact, and will tend to overestimate the significance of the deviations, since it does not take account of the fact that the samples were obtained from a population of finite size. Given equation (1) above, p will have a sampling variance about its equilibrium value for a particular P, and this variance will depend on the population size and will only be zero when the latter is infinite. Equation (1) should strictly be replaced by a probability distribution of p, given P and the size of the population. In the present case, however, the deviations of p and P from their expected values are much too great to be explained by this cause of bias, and it was not considered necessary to apply a more exact test.