REPEATED OCCURRENCES IN THE MOUSE OF LETHAL ALLELES OF THE SAME COMPLEMENTATION GROUP[1]

DOROTHEA BENNETT AND L. C. DUNN

Cornell University Medical College, New York City, and
Columbia University Nevis Biological Station, Irvington-on-Hudson, New York

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THE study of three newly arisen lethal alleles at a complex locus in the house mouse has provided an opportunity to compare the effects of lethal alleles from different sources and especially to compare members of the same complementation group with respect to secondary effects.

The genetics of this locus has been summarized and described recently (DUNN, BENNETT, and BEASLEY 1962). Alleles of three main types have been studied: (1) a lethal, T, with dominant phenotypic effect, $T/+$ being short-tailed; (2) several recessive lethals, t^l, T/t^l being tailless; (3) several viable alleles t^v, T/t^v being tailless and t^v/t^v being viable with a normal tail. The recessives, thus, are recognized as alleles which interact with T to produce a tailless phenotype. They vary among themselves in effects on early development including time of death of lethal homozygotes, in degree of distortion of transmission ratios through sperm, in degree of reduction of recombination near T, in effects on fertility of male compounds, and in effects on viability of compounds in certain combinations.

The questions to be discussed below concern only the second category, the recessive lethals. When two such alleles from different sources such as t^n and t^x complement each other, that is, when t^n/t^x has a normal tail and some degree of viability after birth, then t^n and t^x are assigned to different complementation classes. When, on the other hand, no complementation is detected, and t^n/t^x is indistinguishable in time of death and syndrome of abnormalities from t^n/t^n and t^x/t^x, then t^x is assigned to the same complementation class t^n. These operations are possible with each recessive lethal which forms with T a balanced lethal line, matings within which produce only tailless offspring at birth, i.e. matings $T/t^n \times T/t^n$ produce viable zygotes T/t^n; t^n/t^n, and T/T dying before birth. Where matings between tailless animals from balanced lethal lines with recessive lethals from different sources regularly produce some normal-tailed offspring, these can be shown to be t^n/t^x and the t-alleles concerned assigned to different complementation groups.

The recessive t-lethals available in this laboratory had by these criteria been classified into five complementation groups, designated by the symbol of the first allele in each group to be recognized: t^0, t^9, t^{12}, t^{w1}, t^{w5}. Two questions then arise: Do lethals in the same complementation group differ when examined by other

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criteria? Do recessive lethals at this locus, originating in new independently occurring exceptions, belong to one of the established groups or to additional ones?

These questions bear on the structure of this region of the ninth linkage group. It has been shown that with one exception lethal *t*-alleles interfere with recombination over a length of at least nine crossover units which is the distance between *T* and the nearest marker *tf* (tufted). They are thus presumably connected with some form of chromosomal aberration such as inversion, duplication, or deficiency which interferes with recombination. Furthermore, one *t*-lethal may give rise to a different one. Numerous exceptions of this sort have been analysed and all previously studied ones which arose from balanced lines carrying a marker in this region, e.g. $T\ tf/t^n$ were found to be $t^n tf$. The most likely explanation for the origin of the new alleles is thus exceptional recombination, although with only the marker tufted available a recombinational process cannot in fact be distinguished from conversion or mutation phenomena. If such new alleles were found always to be exact replicates of others previously found, we might be led to suspect that the region consists of a limited number of blocks or units, between which rearrangement may occur by such exceptional recombination. If this were so, the simplest model would predict that the number of blocks would be related to the number of groups of replicate alleles, i.e. the number of complementation groups.

Five criteria may be used in comparing lethal alleles: (1) complementation; (2) embryological comparison; (3) male transmission ratio, i.e. frequencies with which sperm carrying *T* and *t* (in matings of *T*/*t* by +/+) effect fertilization; (4) degree of interference with recombination; (5) degree of complementation when alleles in the same complementation group are combined with lethal alleles belonging to other complementation groups.

These methods have been applied to three lethal *t*-alleles, t^{w21}, t^{w30}, t^{w32}, which were observed in the laboratory to have arisen anew in exceptions from balanced lethal lines. (Alleles are numbered in order of recognition; t^w means derived from an ancestor captured in the wild.)

Origin of the new t*-alleles:* t^{w21} arose from the balanced lethal T/t^{w17} stock (t^{w5} group). It occurred in a single normal tailed t^{w17}/t^{w21} animal from which it was extracted. The marker gene tufted had not at that time been introduced into the T/t^{w17} line, so it is not known whether or not recombination was involved in the origin of t^{w21}.

t^{w30} occurred in a normal-tailed exceptional offspring from the $T\ tf/t^{w12}$ stock (t^{w1} group). Subsequent extraction and genetic analysis showed that the original animal carrying t^{w30} had been of genotype $t^{w12}/t^{w30}\ tf$, and thus indicated that a recombinational process could have been involved in its origin.

t^{w32} arose under conditions which make it difficult to decide whether or not recombination could have been involved in its origin. It appeared in a single tailless animal 16143 of genotype later determined to be $T\ tf/t^{w32}$, which was produced by two presumed $T\ tf/t^{w10}$ animals. The recognition that 16143 carried an allele different from t^{w10} (t^{w5} group) came when it was backcrossed to its father and produced four normal-tailed animals. The stock of t^{w32} was then extracted

from 16143. Its parents were, however, only one generation removed from the wild ancestor which carried t^{w10} and from which the t^{w10} stock was derived. It is possible that the mother of 16143 was not in fact $T\ tf/t^{w10}$ but $T\ tf/t^{w32}$, already carrying the new allele. In that case, t^{w32} might have arisen in the wild parent in the absence of the marker tufted, so that recombination could not be detected. The evidence that the mother was in fact $T\ tf/\ t^{w10}$ rests on the fact that with two different $T\ tf/\ t^{w10}$ males she produced 23 tailless offspring, and no normal tailed ones; with this large number of offspring, it would be unlikely that she carried an allele other than t^{w10}. Most likely, therefore, t^{w32} arose from t^{w10} without detectable recombination. The point is an important one, because if true this would be the only known case of the origin of a *t*-allele without apparent recombination. It may indicate that the *t*-locus extends along a length of chromosome longer than that between the two markers, and that unequal crossing over of the type which may produce new *t*-alleles can take place outside of the marked region.

RESULTS

Establishment of lethality: Tailless lines of genotype T/t^x were established for each one of these three new alleles. The data in Table 1 demonstrate that all three bred as balanced lethal systems, thus proving that each of the new alleles was in fact a lethal.

Complementation tests: Once these new alleles had been diagnosed as lethals, the next step in their identification was to test them for complementation with other known lethal alleles. Representatives of all identified complementation groups were used in these tests. Matings were made between tailless animals of two different genotypes, and the criterion of nonidentity was the production of at least two normal tailed offspring. In some cases much larger numbers were collected to obtain a quantitative estimate of the degree of complementation, but this aspect will be discussed in a later section.

Table 2 shows that t^{w21} declared itself as nonidentical to all alleles except t^{w1}, t^{w3}, t^{w12}, and t^{w20}. These four alleles were already known to be members of the same complementation group and embryologically indistinguishable from one another (BENNETT, DUNN, and BADENHAUSEN 1959). Thus t^{w21} becomes a fifth member of the t^{w1} group.

TABLE 1

Inter-se *matings of tailless animals carrying a lethal allele* t^{w21}, t^{w30}, *or* t^{w32}

Tailless parents	Tailless offspring	Normal-tailed offspring
$T/t^{w21} \times T/t^{w21}$	616	4 t^{w21}/t^{w21}*
		1 t^{w21}/t^{wx}†
$T/t^{w30} \times T/t^{w30}$	171	0
$T/t^{w32} \times T/t^{w32}$	468	1 t^{w32}/t^{w35} tf†

* Typical homozygotes of the t^{w1}/t^{w1} type dead at birth.
† Viable exceptions.

TABLE 2

Complementation tests of lethal alleles t^{w21}, t^{w30} *and* t^{w32} *with other identified lethal* t*-alleles*

	Allele from other balanced lines								
		"t^9 group"			"t^{w1} group"				
	ot^0	ot^9	ot^{w18}	ot^{12}	ot^{w1}	ot^{w3}	ot^{w12}	ot^{w20}	ot^{w5} group
.....	12 nt	.....	7 nt	2 nt	.....	.....	.....	.....	23 nt
ot^{w21}	144 ot	.....	1 ot	3 ot	**29 ot**	**27 ot**	**48 ot**	**28 ot**	68 ot
.....	.....	1 nt*	.....	7 nt	6 nt	.....	3 nt	.....	11 nt
ot^{w30}	.....	**84 ot**	**90 ot**	19 ot	9 ot	.....	5 ot	.....	45 ot
.....	3 nt	.....	3 nt	.....	8 nt	.....	.....	.....	12 nt
ot^{w32}	31 ot	.....	3 ot	**89 ot**	20 ot	.....	.....	.....	18 ot

Figures indicating lack of complementation are printed in bold face. ot = tailless; nt = normal tail.
* This normal tailed animal was studied and proved to be a valid exception of genotype t^9/t^{w40}, t^{w40} being a new viable allele newly arisen in a gamete of the t^{w30} parent.

The allele t^{w30} can be seen to be noncomplementary with both t^9 and t^{w18}. These alleles had previously been found to be indistinguishable from one another on the basis of any of the criteria mentioned in the introduction (P. VAN VALEN, personal communication). It showed complementation with t^{12}, t^{w1} group and t^{w5} group. The t^9 complementation group thus now consists of three members, t^9, t^{w18}, t^{w30}.

The allele t^{w32}, on the basis of the data in Table 2, is seen to complement all alleles except t^{12}. Those two alleles now form the t^{12} complementation group.

On the basis of these complementation data therefore, the three "new" lethals being reported here appeared not to be new, but newly arisen replicates of previously known lethals at locus *T*.

Morphological and embryological comparisons: Once the three lethals had been classified as to complementation group, a comparison of their embryological effects with those of other members of the same group was made. This was done to refine the diagnosis of similarity of noncomplementary alleles, on the assumption that members of the same complementation group may not necessarily show identical or even closely similar effects on development, but still interact to produce a zygote which is lethal before birth.

Four members of the t^{w1} group have been previously reported on in detail; they were seen to produce a syndrome of effects unique among themselves (BENNETT, DUNN and BADENHAUSEN 1959; BENNETT, BADENHAUSEN and DUNN 1959). This group is distinguished among *t*-lethals as having the latest lethal period, and the longest range in time over which death occurs. Death of t^{w1}/t^{w1} individuals occurs sometimes as early as nine days of gestation while others apparently survive until parturition, but are always born dead. From 13 days on, the abnormal embryos present externally a typical picture: they have normal tails, are reduced in size, have microcephaly and always are severely edematous. Since this picture is so typical, we examined litters of embryos from

TABLE 3

Results of dissection of pregnant females from matings $T/t^{w21} \times T/t^{w21}$ *and* $T/t^{w21} \times T/t^{w1}$ *group and diagnosis of embryos found in late period of gestation (13–19 days postfertilization)*

Matings	Total embryos	Normal embryos	Dead (type not recognizable)	Typical t^{w1}/t^{w1} type
$T/t^{w21} \times T/t^{w21}$	119	55	63	1
T/t^{w1} group $\times$ T/t^{w21}	20	9	9	2

matings of $T/t^{w21} \times T/t^{w21}$ and $T/t^{w21} \times T/t^{w1}$ group by gross inspection only, between 13 and 19 days of gestation. The data in Table 3 indicate that both types of crosses produced embryos and stillborn offspring which were indistinguishable from the ones produced by other members of the t^{w1} group. The proportion of abnormal embryos found alive during this period is low, but is about the same as that found for other members of the t^{w1} group.

The t^{w30} allele failed to complement t^9 and t^{w18}. Detailed embryological studies have been published only for t^{w18} (BENNETT and DUNN 1960). t^{w18}/t^{w18} embryos showed a pattern of abnormalities which were based apparently on an overgrowth of the primitive streak and were distinct from any produced by other *t*-alleles. Abnormal embryos clearly showed a bulge in the primitive streak region by seven days of gestation; this overgrowth frequently led, in later stages, to a mechanically produced duplication of the neural tube. Embryos presumed homozygous for t^{w30}, or of genotype t^{w30}/t^{w18} showed exactly comparable disturbances of growth. These embryos were recovered from timed pregnancies derived from matings between $T/t^{w30} \times T/t^{w30}$, and $T/t^{w30} \times T/t^{w18}$; most were studied between seven and nine days when the abnormalities typical of t^{w18} were most easily recognized. Table 4 gives a resumé of the numbers studied and the results.

Another very interesting effect of t^{w18} noted in the previous paper was its effect in promoting the formation of "twin" decidual capsules; these apparently represent implantations occurring so close together in the uterus that a decidual capsule common to the two embryos is formed. Apparently under normal conditions some kind of control mechanism based probably on mechanical agitation by the uterus results in the spacing of preimplantation embryos in the uterus so that when implantation occurs they have the maximum possible distance

TABLE 4

Results of dissections of pregnant females from matings $T/t^{w30} \times T/t^{w30}$ *or* $T/t^{w30} \times T/t^{9}$ *group and diagnosis of embryos seven to ten days postfertilization*

Matings	Total embryos	Normal embryos	*T/T*	Dead (type not recognizable)	t^9/t^9 type
$T/t^{w30} \times T/t^{w30}$	62*	45	2	1	14
T/t^9 group $\times$ T/t^{w30}	93†	46	11	16	20

* Includes five cases of double implantation in one decidual capsule.
† Includes six cases of double implantation in one decidual capsule.

between them (McLAREN and MICHIE 1959). Thus "twin" capsules are rarely formed in litters of normal size; the rate in some of our stocks of the t^{w5} group was six twin capsules in 1209 implants in 165 litters. Matings of t^{w18} mothers however produced nine such double capsules in 685 implants in 82 litters. It appears that this effect is dependent on *maternal* genotype, not on the genotype of the embryos, because the embryos involved in the double capsules are of all possible combinations, namely T/T–T/T, T/T–normal, T/T–t^{w18}/t^{w18}, normal–normal, normal–t^{w18}/t^{w18}, and t^{w18}–t^{w18}.

It now appears that t^{w30} has the same effect. In 15 litters studied from T/t^{w30} mothers mated with either T/t^{w30} or T/t^{w18} males there were ten "twin" capsules. Thus t^{w30} is indistinguishable from t^{w18} both in its effect in homozygous condition on embryonic development, and in its apparent effect in heterozygous condition on preimplantation spacing of embryos.

The "new" lethal t^{w32} forms a complementation group with t^{12}. This is the earliest acting lethal factor yet described in mammals; in homozygous condition it prevents the embryos from making the transition from morula to blastocyst. Also typical of t^{12} homozygotes at the morula stage are abnormally shaped nucleoli, and a deficiency in cytoplasmic RNA (SMITH 1956). Matings were made of $T/t^{w32} \times T/t^{w32}$, and of $T/t^{w32} \times T/t^{12}$ and embryos studied histologically at about 3 to 3½ days after fertilization. This is the period during which, on the average, normal morulae transform into blastocysts. As Table 5 shows, these litters contained two categories of embryos; one of healthy normal blastocysts, and one of pale-staining abnormally organized morulae, which corresponded in every way with the description of t^{12}/t^{12} homozygotes given by SMITH.

TABLE 5

Results of dissections of females pregnant from matings $T/t^{w32} \times T/t^{w32}$ *or* $T/t^{w32} \times T/t^{12}$

Mating	Age of litter	Normal stage of embryos	Number of litters	Number of embryos normal	Number of embryos abnormal	Percent abnormal embryos	Total embryos	Average litter size
$T/t^{w32} \times T/t^{w32}$	7 days	Primitive streak and older	11	55	7*	11.3	62	5.6
	5–6 days	Implantation; preprimitive streak	9	38	4* 2r	13.6	44	4.9
	4 days	Blastocysts; decidual response beginning	8	42	. .	0	42	5.3
	3 days	Free blastocysts	5	14	10m 4u 1d	50	29	6.0
$T/t^{12} \times T/t^{w32}$	3 days	Free blastocysts	9	34	33m 13u	56.5	80	8.9

* = degenerating capsules, r = retarded, m = morulae, u = uncleaved eggs, d = degenerated cells

Litters examined a day later contained only apparently normal embryos. The litter size on the two later days was only slightly more than half its previous value, indicating the death and disappearance of the abnormal morulae. Thus t^{w32} proves to be embryologically indistinguishable from t^{12}.

Transmission ratio comparisons: All lethal *t*-alleles which have so far been studied have an effect in male heterozygotes on the ratio in which they transmit the *t*-allele to their offspring. The transmission ratio can be easily tested by mating males of genotype T/t^n to normal females +/+; the proportion of effective sperm carrying T and t^n can be estimated directly from the proportion of short-tailed ($T/+$) and normal-tailed ($t^n/+$) offspring. Different lethal *t*-alleles are transmitted in widely different ratios, some being as high as 99 percent *t* and some as low as 42 percent *t*.

Table 6 demonstrates that the three different complementation groups under consideration here have average ratios which are clearly different from one another. Within groups, however, the male ratios do not offer any clear evidence for distinguishing one allele as different from another. Variability among different males carrying the same allele is high, especially in the case of alleles such as the t^9 group which show the lowest overall ratio, and this factor makes it difficult to judge which differences are meaningful. The only difference in this group of data which may have meaning is that between t^{w30} and t^{w18}. The difference between a ratio of 42 percent for t^{w30} and 59 percent for t^{w18} is a large one and seems significant. However, the fact that the ranges of transmission ratio for individual t^{w30} and t^{w18} males overlap makes us reluctant to use the difference in average ratio as a criterion of partial genetic difference between these two noncomplementary alleles.

TABLE 6

Comparison of male transmission ratios of t^{w21}, t^{w30}, *and* t^{w32} *with the other* t*-alleles in the same genetic complementation group. Results are shown of testcrosses of tailless* T/t^n *male* × *normal* +/+ *female*

Males tested	Offspring: Total normal tailed (+/*t*)	Offspring: Total short tailed (+/*T*)	Average transmission ratio of *t*	Range* of individual males
T/t^{w21}	248	6	.98	.98–1.00
T/t^{w1}	468	57	.89	.81– .94
T/t^{w3}	392	4	.99	.97–1.00
T/t^{w12}	413	19	.96	.91– .98
T/t^{w20}	227	2	.99	.98–1.00
T/t^{w30}	207	291	.42	.31– .50
T/t^{w18}	420	295	.59	.46– .74
T/t^9	255	302	.46	.24– .70
T/t^{w32}	431	80	.84	.74– .94
T/t^{12}	146	13	.92	

* Ranges indicated only for individual males with at least 50 offspring sampled.

Effects on recombination: Another criterion of similarity which can be used is the effect of lethal *t*-alleles on recombination in their vicinity. All lethal alleles known suppress regular recombination in the *T-tf* interval (about nine crossover units), except for the two alleles, t^9 and t^{w18}, which fall in the same complementation group (DUNN, BENNETT and BEASLEY 1962). It has now been found that t^{w30} also permits some recombination, 6/121 animals scored, in this interval. The fact that only the three members of this group permit recombination in their region may be taken as additional evidence of their similarity.

Complementation tests of the t^{w1} *group alleles with* t^0: A fourth method by which noncomplementary alleles can be compared is their degree of complementation with other lethal alleles. Although two lethal alleles must be considered complementary and therefore nonidentical if they produce any normal-tailed (t^x/t^n) compounds at all, it has been found that as a rule complementation is not complete. In other words, the proportion of normal-tailed compounds found at birth is in most cases less, sometimes considerably less, than the expected proportion. Thus complementation in this situation can be estimated quantitatively.

When the five members of the t^{w1} group were crossed with stocks containing t^0 (e.g. $T/t^{w1} \times T/t^0$) each test resulted in a diagnosis of complementation because of the appearance of normal-tailed compounds (e.g. t^{w1}/t^0). Table 7 shows, however, that the degree of complementation of the first three alleles (each tracing directly to a heterozygote captured in the wild) differs strikingly from the very low degree characteristic of both of the last two alleles each of which arose in an exception from a balanced line carrying a lethal allele of the t^{w5} group. We have no evidence that this sharp difference is due to the difference in manner of origin of these alleles but it suggests that t^{w20} and t^{w21} resemble each other in some property which distinguishes them, as a kind of subgroup of the t^{w1} group.

DISCUSSION

The chief outcome of our complementation studies has been to show that each of three newly arisen lethals resembles the lethals in one of the complementation groups which had already been recognized. This shows that the numbers of complementation groups with the properties of *t*-alleles is definitely limited. Although

TABLE 7

Complementation tests of alleles of the "t^{w1} *group" by* t^0. *Results of matings of* T/t^{w1} *group males (tailless) with* T/t^0 *(tailless) females*

Allele	Offspring with normal tails	Tailless	Expected proportion of normal tailed young	Observed proportion of normal tailed young	Percent of expected proportion found
T/t^{w1}	51	77	.47	.40	85
T/t^{w3}	21	26	.50	.45	90
T/t^{w12}	10	25	.49	.29	59
T/t^{w20}	11	179	.50	.06	1.2
T/t^{w21}	12	144	.50	.08	1.6

20 balanced lethal lines (T/t^n) have been examined embryologically and genetically we have found only five different (i.e. complementary) groups of t-lethals: t^0, t^9, t^{12}, t^{w1}, t^{w5}. Twelve of the 20 lines studied contained alleles taken from different wild populations, and thus some of these may trace to a common ancestral allele which underwent dispersion. However, seven lines originated under observation in exceptions from known balanced lethal lines, and the t-alleles in these are thus known to be of independent origin. Of these seven, only two (t^9 and t^{12}) established new complementation groups, while five appeared to be recurrences (usually by apparent recombination) of lethals already identified. If five out of seven lethals known to be of independent origin turn out to be recurrences, then the total potential number of complementation groups is surely quite small.

This conclusion was partially confirmed by comparison of other properties of alleles which on genetical and embryological grounds had been assigned to the same complementation group.

In general, two of the three subsidiary effects of derived alleles, those on transmission ratio and recombination, were all indistinguishable within complementation groups and did not provide a basis of judgement sufficient for proving differences among lethal alleles in one group.

With respect to the strength of complementation interactions, however, the members of one group (t^{w1}) appeared to have attributes which were not identical. Two of the alleles in that group (t^{w20} and t^{w21}) showed a very marked difference in their ability to complement t^0, as compared with the other three members. It seems unlikely that a difference of the magnitude observed can be explained by factors extraneous to the t-locus such as background genotype or different degrees of heterosis produced by crossing different lines. We feel that the most likely hypothesis is a structural difference among the alleles of that group which is reflected detectably only in their complementation reactions with t^0. If we return now to the idea of deficiency or duplication, we might postulate that t^{w20} and t^{w21} include the same region as t^{w1}, t^{w3} and t^{w12}, but are slightly more extensive and extend into the t^0 region so as to be partially overlapping with it. On this hypothesis embryos t^0/t^{w20} and t^0/t^{w21} would be homozygous for a defective region common to both t^0 and t^{w20}–t^{w21} and their prenatal viability because of this should be lower than that of t^0/t^{w1}, t^0/t^{w3}, or t^0/t^{w12}.

The tentative conclusion to be drawn from this type of study is that some complementation groups at the t-locus may be broken down into subgroups on the basis of specific other criteria, and consequently that the chromosomal basis for different members of lethal t-allele complementation groups may not be identical.

SUMMARY

Three lethal t-alleles, each originating from an exceptional offspring t^n/t^x from a balanced lethal tailless line $T/t^n \times T/t^n$ were compared with respect to embryological effects, genetical behavior, male transmission ratio and effect on recombination near the T locus. Each allele was found to be indistinguishable on these

criteria from the members of one of the five *t*-lethal complementation groups already known.

These observations were taken to support the view that the chromosome region within which the *t*-lethals occur is subject to structural change (e.g. deficiency or duplication) connected with exceptional recombination occurring at a limited number of points, since five out of seven independently arisen lethals represent recurrences of aberrations previously observed.

In addition, two members (t^{w20} and t^{w21}) of one complementation group differed widely from the other three members (t^{w1}, t^{w3}, t^{w12}) in the degree of complementation with a different lethal (t^0) as judged by the proportion of compound embryos which survived to birth. This was taken as an indication that the extent of aberration (e.g. deficiency or duplication) may differ amongst members of the same complementation, and in some cases may partially overlap the area of aberration characteristic of a contiguous complementation group.

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