INHERITANCE OF AUDIOGENIC SEIZURE SUSCEPTIBILITY IN THE MOUSE

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HALL (1947) has reported a remarkable difference between dba and C57 black mice in their susceptibility to audiogenic seizures. When dba mice are placed in a metal tub and stimulated by the sound of a doorbell, the majority undergo violent tonic-clonic seizures which are usually fatal. The incidence of such seizures in the C57 black strain is very low. These convulsions appear to be similar to audiogenic seizures occurring in rats, which have been recently discussed by FINGER (1947). Similar convulsions have been reported in Peromyscus (DICE 1935; WATSON 1939) where susceptibility has been considered due to recessive genes. In 1949 WITT and HALL attributed seizure susceptibility in the house mouse to a single dominant gene which they called *As*. This hypothesis was based upon the results of the F_1, F_2 and the two backcross generations. Only their "critical backcross" of $F_1 \times$ C57 bl non-reactors by C57bl failed to accord with their single dominant gene hypothesis. Twenty-five percent of these animals underwent mild convulsive behavior which the authors attributed to minor modifying genes. GINSBURG, MILLER and ZAMIS (1950) have postulated two or more non-dominant factors, including a single major gene essential for seizure susceptibility.

The clearcut strain difference makes these animals admirably suited for investigations of physiology of convulsions, and the physiological genetics of susceptibility. GINSBURG and HOVDA (1947) in the course of studying the metabolic differences between strains, noted that one strain of dba's recovered from seizures more readily than the regular Jackson Laboratory stock of dba's. These animals were descended from a female which had developed in the uterus of a C57 bl female following an ovum transfer. They suggested that a nongenic maternal influence might affect recovery. The experiments described in this paper were initiated to test this hypothesis by comparing reciprocal crosses. The preliminary results were not in accordance with the single dominant gene hypothesis, and a series of experiments was initiated on the factors producing variability in the risk of convulsions in hybrids.

METHODS

The subjects of this experiment were C57 black subline 6 Jax mice descended by brother-sister matings from WITT and HALL'S original strain. The dba mice were of subline 2 and had been inbred for over 50 generations. WITT and HALL used dba subline 1, and it has been shown that the authors' subline has an even higher susceptibility than HALL'S original stock.

The stimulation method used was identical to that of WITT and HALL except that behavior observations were not made for a two-minute period following bell ringing, and each animal, provided it survived that long, was

exposed on five successive days (instead of four) to two minutes of bell ringing. The mice were 30 days of age on the first trial day except for F_2 animals which were started on Mondays at an age of 29 to 35 days.

Our index of seizure susceptibility differs from that of WITT and HALL. These investigators classified each animal as a "reactor" or "non-reactor." A "reactor" was defined as an animal which convulsed on any one of its four trials. Their tables show 93.3 percent of the dba stock to be "reactors," and 94.7 percent of the C57 black stock to be "non-reactors," while the F_1 mice included 94.5 percent of reactors. These figures indicate that the convulsion phenotype does not always follow the genotype, and that a classification of genotypes on their basis cannot be expected to be accurate to better than ± 5 percent. It seems to be more satisfactory to define seizure susceptibility in terms of the risk of an induced convulsion during a standard exposure. This risk cannot be determined on one individual, but it can be calculated for populations of different genotypes. Since the percentage of convulsions is usually highest on first exposure, the first exposure seizure risk is the best single index of susceptibility. In estimating this value all convulsions of any degree of severity are included, but preconvulsive activity, such as hopping or wild circling, is not. The percentage of seizures among survivors of the first trial on successive trials is of physiological and genetic interest, particularly when dealing with genetically heterogeneous groups such as the F_2, F_3 and backcrosses.

RECIPROCAL CROSS AND SEX DIFFERENCES

The principal results of this investigation are summarized in table 1, which gives the percentage of convulsions and of deaths for each group of mice studied. No statistically significant differences have been found between reciprocal crosses and they have been grouped together in all summarizing tables. There are nine possible pairings of male and female subjects with the same genetic background. If the comparison is based upon the percentage of "reactors" (WITT and HALL'S criterion), males have a higher percentage in three pairings, females in three, and the remaining three cases are equal. If the comparison is based upon first trial seizure risk, the males are higher in five cases, females in two, and two are equal. The most extreme sex differences are found in the $F_1 \times$ C57 black backcross and F_1 hybrids. In the latter group females showed a higher susceptibility than males. This particular group of mice appears to be exceptional and will be discussed below. In fact, a repeat sample of F_1's included on the last line of table 1 shows a strong reversal of the sex difference. The effect of sex on susceptibility appears to be influenced by the genotype of the individual. It is unimportant in genotypes with very high or very low susceptibility, and influential in genotypes of moderate susceptibility.

THE SINGLE DOMINANT GENE HYPOTHESIS

If the sexes and reciprocal crosses are combined, as in table 2, it is possible to compare these results with those of WITT and HALL. The two parent strains

TABLE 1

Incidence of convulsions (C) and death (D) from convulsions in dba, C57bl, and hybrids

FEMALE P	MALE P	SEX	N	PERCENT CONVULSERS	TRIAL 1			TRIAL 2			TRIAL 3			TRIAL 4			TRIAL 5			TRIALS 1–5			D/C ×100	% SURVIVORS
					N	%C	%D	N	%C	%D	N	%C	%D	N	%C	%D	N	%C	%D	N	%C	%D		
dba	dba	F	41	100	41	98	85	6	83	33	4	100	100							45	96.1	80.4	87.0	0.0
dba	dba	M	54	100	54	100	87	7	100	57	3	33	33	2	50	50	1	0	0	67	94.0	79.1	84.7	2.0
F_1	dba	F	59	97	59	90	54	27	33	19	22	41	5	21	48	5	20	50	5	148	60.8	26.3	43.2	32.3
F_1	dba	M	69	93	69	93	61	27	70	22	21	57	10	19	58	10	17	47	0	152	74.3	33.5	45.1	24.6
dba	F_1	F	31	94	31	87	65	11	55	27	8	38	0	8	63	13	7	29	0	65	66.2	37.0	55.8	22.6
dba	F_1	M	32	100	32	97	47	17	59	30	12	75	8	11	73	9	10	40	20	82	75.7	29.3	28.7	25.0
dba	C57	F	25	76	25	32	16	21	10	0	21	33	19	17	47	12	15	40	0	99	31.3	10.1	32.0	60.0
dba	C57	M	25	52	25	20	12	22	18	14	19	26	5	18	22	6	17	29	0	101	22.3	7.9	35.4	68.0
C57	dba	F	25	84	25	48	20	20	20	10	18	56	6	17	53	12	15	60	13	104	45.8	12.8	27.9	52.0
C57	dba	M	25	64	25	28	8	23	26	13	20	45	10	18	22	0	18	22	6	94	29.9	7.7	25.7	68.0
F_1	C57	F	49	37	49	18	10	44	2	2	43	5	2	42	2	0	42	14	7	220	8.2	4.1	50.0	79.6
F_1	C57	M	35	37	35	29	20	28	11	4	27	11	7	25	4	0	25	8	0	140	13.5	7.1	52.5	71.5
C57	F_1	F	37	24	37	16	14	32	9	3	31	0	0	31	3	3	30	0	0	161	6.2	4.3	71.0	81.2
C57	F_1	M	30	37	30	30	23	23	4	4	22	5	0	22	9	5	21	5	0	104	11.8	7.6	64.3	70.0
F_1	F_1	F	55	69	55	60	29	39	41	5	37	30	0	37	32	3	36	31	6	204	40.7	10.3	25.3	61.8
F_1	F_1	M	57	70	57	60	40	33	27	9	30	17	3	29	24	10	26	12	0	175	33.1	17.1	51.7	45.6
C57	C57	F	25	0	25	0	0	25	0	0	25	0	0	25	0	0	25	0	0	125	0	0	—	100.0
C57	C57	M	25	0	25	0	0	25	0	0	25	0	0	25	0	0	25	0	0	125	0	0	—	100.0
(dba)†	(C57)	M	73	79*	79	74	51	17*	6*	0*	17*	12*	6*	16*	13*	0*	16*	31*	0*	104*	35.6*	21.2*	59.6*	42.1*
(C57)	(dba)	F																						

* Based upon a subsample of 38 F_1 animals.

† This is referred to as the "repeat" F_1.

TABLE 2

Summary of selected results by genetic groups.

GROUP	N	PERCENT CONVULSERS 5 TRIALS	PERCENT* "REACTORS" WITT & HALL 4 TRIALS	TRIAL 1		TRIAL 1 D/C	PERCENT SURVIVORS 5 TRIALS
				% C	% D		
dba	96	100	93.3±4.7	99	86±3.5	87±3.5	1
F_1×dba	191	95 ±1.6	90.9±6.1	92±2.0	57±4.6	62±3.7	27 ±3.2
F_1 "original"	100	68 ±4.7	90.5±3.3	32±4.7	14±3.5	44±8.8	62 ±4.9
F_1 "repeat"	73	79†±6.6	90.5±3.3	74±4.9	51±5.8	69±6.3	42†±8.0
F_2	112	70 ±4.3	77.3±5.0	60±4.6	35±4.5	58±6.0	53 ±4.7
F_1×C57bl	151	34 ±3.8	52.8±6.0	23±3.4	16±3.0	70±7.7	76 ±3.5
C57 bl	50	0	5.3±3.6	0	0	0	100

* Data from WITT and HALL (1949)

† Based upon a subsample of 38 cases.

which were used differ more widely than those of WITT and HALL, and all hybrids except the F_1×dba have a lower percentage of "reactors" than these authors obtained. It should also be noted that hybrids which would be expected to behave like dba's under the single dominant gene hypothesis (F_1×dba and F_1) actually differ considerably, particularly if death-convulsion ratios and percentage of survivors of five trials are taken into consideration.

Both the "original" and "repeat" samples of F_1 are intermediate in susceptibility between the parental strains. It is probable that the repeat group is more representative of the total F_1 population. The original F_1 sample is exceptional in having a higher susceptibility in females than in males, in not showing the highest seizure incidence on the first trial, and in not fitting into the progression of susceptibility indices. If the F_1 repeat group replaces the original sample, indices of susceptibility are seen to decrease regularly in relation to the proportion of dba genes contained in each group. The single dominant gene hypothesis may be formally tested by calculating χ^2 for the F_2 and F_1×C57bl groups on the assumption that all animals carrying this gene will convulse within five trials and 99 percent of them will convulse on the first trial.

The values marked with asterisks are significant at better than the 1 percent level, so that the dominant gene hypothesis may be rejected for this particular cross.

GROUP	CONVULSE WITHIN 5 TRIALS				CONVULSE ON FIRST TRIAL		
	N	EXPECTED	OBSERVED	χ^2	EXPECTED	OBSERVED	χ^2
F_2	112	84	78	1.72	83	66	13.41*
F_1×C57bl	151	75.5	51	14.9*	75	35	43.7*

We may now examine the evidence as it relates to the number of genes involved. Will a single gene producing high susceptibility in homozygous animals and moderate susceptibility (74 percent) in heterozygous animals

explain the results? In calculating expected values under this assumption the F_1 repeat group is taken as the standard for the heterozygote. The calculations may be summarized as follows:

	GENOTYPES	FIRST TRIAL SEIZURE RISK CALCULATED	OBSERVED
F_1×dba	1/2 *AA*, 1/2 *Aa*	(99+74)/2=86.5	92±2.0
F_2	1/4 *AA*, 1/2 *Aa*, 1/4 *aa*	(99+2(74)+0)/4=61.8	60±4.6
F_1×C57bl	1/2 *Aa*, 1/2 *aa*	(74+0)/2=37.0	23±3.3
		CALCULATED TOTAL CONVULSIONS	OBSERVED
F_1×dba	1/2 *AA*, 1/2 *Aa*	(100+79)/2=89.5	95±1.8
F_2	1/4 *AA*, 1/2 *Aa*, 1/4 *aa*	(100+2(79)+0)/4=64.5	70±4.6
F_1×C57bl	1/2 *Aa*/ 1/2 *aa*	(79+0)/2=39.5	34±3.9

Except for the first trial seizure risk for the F_1×C57, the calculated and observed risks do not differ more than might be explained by errors of random sampling and the occurrence of modifying genes. The assumption of a single major partially-dominant convulsing gene is not contraindicated by these data.

As WRIGHT (1934) has pointed out, however, the occurrence of expected ratios in the F_1, F_2, and backcross generations is not a certain proof of single gene control. An attempt was made to utilize WRIGHT'S procedure for estimation of the number of genes involved, by comparing the percentages of 1) non-convulsions, 2) convulsions and recovery, and 3) convulsions with death, in the various populations. The method proved inapplicable because of the fact that some populations include too few members in some of the three classes. Also, evidence described below favors a hypothesis that death from convulsions does not merely result from a more severe convulsion or a greater seizure susceptibility. The strongest evidence in favor of a multiple gene hypothesis is the fact that three matings of non-convulsing F_2 animals yielded an F_3 which is practically identical in seizure risk to the F_1×C57bl group. This small sample (n=17) includes two subjects dying on the first trial, nine resisting five trials, one which recovered five times from severe convulsions, and five others which convulsed at least once. Certainly genes lowering resistance were well distributed in this group selected on the basis of successfully withstanding five exposures without convulsions. The results are most simply interpreted by a multiple factor hypothesis under which the number of susceptibility genes determines seizure risk. Animals in the F_2 having low genetic seizure risk may produce offspring with a high risk through segregation and recombination. Very large samples of F_2 and F_3 subjects must be available, however, to provide a critical test for the number of gene pairs involved, because of the fact that in low dilution there is at present no way to distinguish these genes. In fact, the detailed genetics must await a method of classifying

phenotypes which is based upon a quantitative unit of susceptibility, not a simple dichotomy into convulser or non-convulser.

THE PHYSIOLOGICAL GRADIENT OF SUSCEPTIBILITY

It has been shown above that there is no simple correspondence between genotype and phenotype in respect to audiogenic seizure incidence. This is well demonstrated in the genetically homogeneous F_1 which is extremely variable in seizure susceptibility. Furthermore, seizure susceptibility is not constant in one animal from day to day. One mouse may resist four exposures and die on the fifth, another may convulse and recover on the second exposure and be resistant on four other trials, while still another convulses and recovers five times. If one interprets the data from a statistical point of view, it must be concluded that the genotype actually determines the proportion of time during which an individual is susceptible. Mice of our dba subline 2 strain are almost always susceptible, the C57 blacks practically never susceptible, and the F_1's susceptible somewhere between 32 percent and 74 percent of the time. The extreme variability of the F_1's is, in fact, predictable on the basis of the hypothesis that what appears to be a character of alternative expression is in reality a quantitative character which varies over a wide range. The assay of this character by bell ringing merely divides the group into animals above and below a threshold at the moment of testing. Thus, the mode of inheritance appears to parallel that found by WRIGHT (1934) for polydactyly and WRIGHT and WAGNER (1935) for otocephaly in the guinea pig, and by HESTON (1942a and b) for lung cancer in mice. Audiogenic seizure susceptibility differs from these examples because no gross structural changes have been found, nor is any individual absolutely committed to a definite position on the scale. Susceptibility may shift up and down in an apparently random manner during the five day test period. However, this shifting apparently occurs within genetically prescribed limits which are the same for all members of the same genotype. In the repeat F_1 group the probability of not seizing on the first trial is 0.26 and of not seizing on any one of trials 2 to 5 is 0.85. The probability of not seizing on any trial is $0.26 \times 0.854 = 0.222$. The expected number of non-convulsers in 5 trials for the sample of 38 is 8.36, and the observed value, 8, is not significantly different.

If the non-genetic factors operate in a random manner, each genotype should include members grouped symetrically about a mean value of susceptibility. The curves of figure 1 express these relationships graphically. The abscissae represent differences of susceptibility in units of the standard deviation (t units), while the ordinates are arbitrarily drawn so that the area under each curve equals unity.

A genotype with a convulsive risk of 50 percent would have its midpoint at zero on the scale; genotypes with less resistance will have their midpoints in the negative region. At any moment in time a cross section of the genotype will yield seizure susceptible animals in proportion to the portion of the area under the curve lying to the left of the threshold. Individual animals, however, at different points in time shift their relationship to the threshold.

External conditions such as temperature, and the degree of restraint or mechanical agitation have been shown in preliminary experiments to affect seizure susceptibility. Such factors may be considered to move the population as a whole to the right or left along the susceptibility axis. Figure 1 demonstrates that changes of this sort influence the seizure risk of F_1 hybrids much more than the parent strains. The parents are assumed to be 6 t units apart and the F_1 to be exactly intermediate. The "normal" position of the F_1 in figure 1a is based upon the repeat F_1 sample. A convulsant agent is assumed in figure 1b to shift all curves to the left by one unit; and in figure 1c an anticonvulsant agent shifts them all one unit to the right. The parental values are arbitrarily selected, as the data to locate them exactly are not available. The

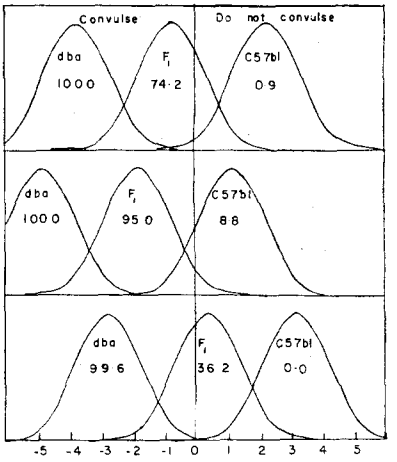

FIGURE 1. Changes in convulsive risk on first trial (figures under curves) associated with conditions shifting physiological susceptibility by one standard deviation. The abcissa is a scale of physiological susceptibility. Each genotype is assumed to vary normally about some point on this scale. The convulsive risk is dependent upon the proportion of the curve to the left of an arbitrary threshold. (a) The upper section represents the situation in the 'repeat' F_1; (b) the middle section approximates the results obtained by Witt and Hall; (c) the lower section approximates the results in the authors' 'original' F_1.

striking fact is that a change which greatly affects the hybrid is relatively unimportant to the parents. This accords with the observed agreement between investigators with respect to the susceptibility of the parent strains, and the variability between different samples of the hybrids.

The writers are unable to explain the discrepancy between their own "original" and "repeat" F_1 groups. The procedure for each was supposed to be the same, though the testing was done by a different person in a different room at a different time of year. Presumably some subtle environmental influence was responsible. Figures 1a and 1c approximately represent the two samples. Figure 1b approximates the WITT and HALL data which were obtained from a different subline of the dba strain.

COMPARISON OF CONVULSION RISK AND DEATH RISK

In the discussion of results thus far, only the incidence of convulsions has been considered. The hybrids, however, differ from the dba stock in another particular, the ability to recover from an induced seizure. Eighty-seven percent of convulsing dba's die on the first trial, and only one percent survive five trials. The dba backcross has nearly as high a convulsion risk as the dba, but only 62 percent of the first trial convulsers die, and 27 percent survive five trials. Data for the other hybrids are included in table 1.

The lowered death rate could be due to 1) less severe convulsions, 2) to an increased stress resistance in the hybrids, derived presumably from the C57 bl line, and 3) to a combination of these factors. The fact that the first trial death/convulsion ratio is so constant in the hybrids, although the incidence of seizures varies widely, is evidence in favor of a separate gene system influencing stress resistance. It is impossible to secure direct evidence on the ability of C57 blacks to recover from audiogenic seizures, since the incidence is so low. However, convulsions can be induced in C57 black mice by applying alternating current to the head. Electrogenic convulsions have many features in common with audiogenic convulsions, and in some strains of mice frequently result in death (STONE, EADY, and HANTY 1949). MR. A. J. COULOMBRE, working in the authors' laboratory, has determined the death/convulsion ratio in C57 bl mice at 30–40 days of age. Twelve mice given 7.5 milliamperes through electrodes applied to their ears convulsed, and five died. Although the sample is small, the rate of recovery from E.C.S. in C57 bl appears to be definitely higher than the rate of recovery of dba mice from audiogenic seizures, and is comparable to the rate of recovery in dba×C57 hybrids. Furthermore, observation indicates that animals may recover from long severe seizures, and die from seizures of apparently lesser intensity. Only mild forms of seizure involving hind limb paralysis without falling on the side never result in death.

Further evidence of independence of susceptibility and recovery has been obtained from a study of seizure latency. The interval between the onset of each convulsion and the beginning of the stimulus was recorded to the nearest second. The distribution of latencies is given in table 3. It is clear that the seizure latencies in the F_1 and $F_1 \times C57$ are significantly higher than in dba or $F_1 \times$dba. The two latter groups have a bimodal distribution of latencies,

TABLE 3

Distribution of seizure latencies for first three trials.

GROUP	LATENCY IN SECONDS										N	M
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99		
dba	1	20	3	32	43	9	—	—	—	—	108	35.8±1.2
$F_1 \times$dba	2	24	12	83	90	29	9	—	—	—	249	38.9±0.8
F_1	—	—	1	2	12	44	15	3	—	1	78	55.2±1.1
F_2	2	1	—	16	47	13	2	1	—	—	82	43.6±1.1
F_1xC57	—	—	—	2	18	14	8	4	2	—	48	54.5±1.7
Total	5	45	16	125	210	109	34	8	2	1	565	—

and there is a hint of bimodality in the F_2. The cause of this bimodality in the highly inbred parental strain presents an interesting problem for future experimentation. The data of table 3 are wholly consistent with the hypothesis that average seizure latency is an index of physiological susceptibility to audiogenic seizures. The distribution of the latencies is consistent with the hypothesis that the dba parent contributes genes reducing latency and the C57 parent contributes genes increasing latency. When these genes produce latencies of more than 80 seconds, convulsions seldom result. Hence the seizure latency of the C57 backcross is essentially the same as the F_1, although the seizure risk is much less.

Is seizure latency also related to death risk? An analysis of variance according to the genotype and outcome was carried out with the dba and F_1 hybrids. The results, summarized in table 4, show that only the difference between genotypes is significant, and there is no relationship between fatal or non-fatal outcome and latency. Convulsion risk and death risk once a convulsion is initiated depend upon different physiological mechanisms.

DISCUSSION

The findings reported here provide a basis for reconciling divergent results on the seizure susceptibility of dba and C57 bl hybrids. Although the con-

TABLE 4

*Analysis of variance of seizure latency according to genetic group and outcome of convulsions.**

	dba		F_1		W	D
	n_1	$\bar{x}_1$	n_2	$\bar{x}_2$		
Recover	27	34.4	59	54.7	18.52	20.3
Die	117	34.7	45	53.7	32.50	20.0

* In the analysis of variance calculated below $\bar{x}$ and D have been coded by dividing by 5. Correction for disproportion in the subclass numbers has been made according to SNEDECOR (1946, p. 284).

SOURCE OF VARIATION	d.f.	SUM OF SQUARES (UNCORRECTED)	CORRECTION FOR DISPROPORTION	MEAN SQUARE
Genetic	1	921.61	147.84	773.77
Outcome	1	156.43	147.84	8.59
Interaction	1			0.80
Individuals	246	1152.16		4.68

F (for genetic variance) = 773.77/4.68 = 165.33 (Significant at better than 1 %)
F (for outcome) = 8.59/4.68 = 1.83 (not significant)
F (for interaction) = 0.80/4.68 = 0.17 (not significant)

* Additional cases have been added to those reported in table 3 so that the numbers and means differ slightly. With respect to seizure latency the "original" and "repeat" F_1 samples are the same.

clusions presented here regarding the type of genic control of susceptibility differ from those of WITT and HALL, their data are perfectly consistent with the hypothesis presented. Subline differences may be expected to shift populations along the axis of physiological susceptibility, and the effect upon seizure risk will depend upon the particular region in which the shift occurs. Another probable cause of variation in results with hybrids, is the expected greater sensitivity of genotypes near the threshold to environmental influences. Evidence has been presented to show that such influences may be subtle, and hard to detect even when all ordinary precautions are taken.

The clear separation of seizure risk and death risk is of importance in considering the significance of experiments on the physiology of seizures. GINSBURG and co-workers (1947; in press) have reported several agents which protect against death without altering seizure incidence. It is almost certain that these operate on the recovery mechanism rather than on the physiological gradient of susceptibility postulated in this paper. Since the protective agents are related to modification of brain metabolism, it is probable that resistance to death from seizure depends upon the ability of the brain to sustain metabolism during the anoxia produced by the cessation of respiration at the climax of the convulsion.

The only clue to the nature of the physiological gradient of susceptibility is in the relationship of susceptibility and seizure latency. If one assumes that impulses entering the central nervous system over the auditory nerve cause the accumualtion of a substance or produce a polarized state, then differences in the rate of removal or destruction of the substance or leakage of electric charges would have an effect on the amount of time needed to reach a threshold. If the rate of destruction were sufficiently rapid the threshold would never be attained. Further speculation is of little value until experiments are designed to test this hypothesis.

SUMMARY AND CONCLUSIONS

1. A study of audiogenic seizure susceptibility has been made in hybrids between dba subline 2 and C57 bl subline 6.

2. Susceptibility to sound induced convulsions is probably due to multiple factors although the F_1 and F_1 backcross generations contain susceptible animals in proportions which approach those which would be expected on the basis of a single gene showing incomplete dominance.

3. The gene system producing susceptibility determines the position of an animal on a physiological gradient of susceptibility.

4. The ability to recover from a sound-induced seizure is also inherited, but is independent of seizure susceptibility.

5. The latency of seizure onset is related to convulsion risk, but not to death risk.

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