Behavior associated with age and audiogenic seizures in an inbred strain of mice

By

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A thesis

Submitted in partial fulfillment of the requirements for the degree of Master of Arts in Drake University

Des Moines, Iowa
January, 1952
To My Wife

Florine Wright Bruce
ACKNOWLEDGEMENTS

The writer wishes to express his gratitude to Professor Joseph R. Royce for his suggestions and sincere criticism throughout the course of the investigation; to Dr. Frank C. Coleman, Director of the Department of Pathology at Mercy Hospital, for his cooperation in assisting in the preparation and microscopic examination of the brains of mice; to Dr. Anthony C. Westerhof and Dr. Leonard Towner for their sympathetic and helpful criticism; to Dean Byrl Benton and Dr. Leland Johnson for the use of facilities in Fitch Hall of Pharmacy and Harvey Ingham Hall of Science; and to Charles Ballinger for his assistance in caring for the experimental stock.
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CHAPTER I

INTRODUCTION

Behavior disorders or so-called "experimental neuroses" have been observed by many investigators in a variety of species. Finger indicates that convulsive behavior has been studied experimentally in such mammals as the cat, dog, mouse, rabbit, and pig. Hall and Martin refer to behavior disorders in the chimpanzee and rat. So far as is known only rats and mice have been found susceptible to audiogenic seizures. It has been found by many investigators that abnormal behavior may be elicited by a variety of stimuli such as conflict, sound, electric shock, drugs, and dietary deficiency.

Although the literature appears to indicate that a variety of species and stimuli have been used in experimental investigation, "the rat continues to hold its pre-eminent position as an animal in laboratory investigation." It is for this reason that the writer has found it necessary to refer to studies in which the rat has been used.


In this paper the writer has attempted to confine his investigation to behavior associated with age and audiogenic seizures in an inbred strain of mice. The age factor was selected for investigation because there appears to be little published evidence concerning the influence of this factor on audiogenic seizures.

A particular inbred strain of mice was chosen as experimental stock, since there was evidence that this strain was known to be adequately susceptible to auditory stimulation. Hall,\(^1\) while pursuing research at the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine, made the discovery of this highly susceptible strain. It has also been found that these strains of mice vary considerably in the degree of susceptibility to auditory stimulation. Hall\(^2\) has found that at a given age, one strain of mice will convulse and die, while another crouches and "freezes" during auditory stimulation.

The strain chosen for this investigation is reported to have been inbred for many hundreds of generations; thus, the stock may be considered relatively free from individual differences. The strain used in this investigation is known as the dilute brown non-agouti or (dba). These animals were (dba) subline 2 stock, obtained from the Supply Department of the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine. These animals were used in raising the experimental stock for this investigation. Scott indicates that subline differences


appear to be extremely important. He states that "care should be taken that the animals used come from an inbred stock, tracing back through a single line of brother-sister mating as pedigreed by known workers." Subline 2 stock has been pedigreed by Little, Woolley, and Vicari.

The influence that age may have on audiogenic seizures in the rat has been investigated by several workers. Finger found that in some rats,

... the increase of age beyond a certain point was accompanied by a decline in susceptibility. Further age increments decreased still further the percentage of susceptible rats, although some rats continued to exhibit the full convulsive pattern at 510 days. Finger also states that, "with increasing age, a number of vital physiological alterations take place in the organism," and refers to investigations by Dice, Farris and Yeakel, Maier, and Glaser. Morgan refers to the age factor in his discussion of the latency of audiogenic seizures.

The behavior disorder investigated here and previously referred to as "experimental neurosis" was originally called a "neurotic pattern" but has been renamed "audiogenic" seizure by Morgan and Waldman and an

1J. P. Scott, "The Use as Test Material of Inbred Strains of Mice Having High Frequencies of Audiogenic Seizures," Science, CXI (May, 1950), 583.

2F. W. Finger, "Factors Influencing Audiogenic Seizures in the Rat, II. Heredity and Age," The Journal of Comparative Psychology, XXXV (April, 1943), 232.

3Ibid., p. 220.


"audio-epileptic" seizure by Smith.¹ Throughout the course of this paper the term audiogenic or convulsive seizure will be employed interchangeably.

The behavior observed in an audiogenic seizure is episodic and convulsive in nature. It appears to consist of sudden, violent, and undirected running, jumping, stiff hopping, and tonic and clonic manifestations; this is followed by an inactive, comatose phase during which there is a lack of response to sensory stimulation, reflexes and righting responses are absent, and the animal may be molded in any direction. The active period of the attack is brief, usually lasting less than thirty seconds. The passive phase may persist for a minute or longer, with gradual return to apparent normality.

In this investigation the stimulation which evoked the seizure was produced by a doorbell suspended on the inside of a standard galvanized tub. A circular paper blotter was placed on the bottom to absorb some of the vibration caused by the ringing bell. The apparatus employed was similar to that used by Hall.²

It appears that some relationship may exist between the abnormal behavior observed in animals and that observed in human subjects. A few investigators venture a comparative observation. Margaret L. Watson states that, "the epilepsy which occurs in Peromyscus is a particularly important character for study, because it is closely similar to certain

¹K. U. Smith, "Quantitative Analysis of the Pattern of Activity in Audio-epileptic Seizures in Rats," The Journal of Comparative Psychology, XXXII (June, 1941), 311.

²Hall, op. cit., p. 3.
types of epilepsy in man."\(^1\) Anastasi and Foley\(^2\) suggest that a study of seizure behavior in animals may facilitate an understanding of such human problems as epilepsy and shock therapy. Hamilton\(^3\) has compared convulsions in the rat with the symptomatology of human epilepsy. The writer has made no effort, beyond citing the literature, to explore this relationship.

While carrying out the investigation, the writer had the opportunity to prepare the brains of ten control and ten experimental animals for sectioning. These brains were sectioned, stained, and examined for anatomical differences. Dr. Frank C. Coleman,\(^4\) who made the examination, found no observable anatomical changes in brain tissue in either the control or experimental groups. The writer felt that some evidence of brain destruction or lesions might be observed as a consequence of the violent convulsive seizures. Since no evidence of change was observed in the brain tissue, further investigation of cause and effect may be necessary.

The writer has made no effort to investigate the underlying conditions for an audiogenic seizure. Lindsley, Finger, and Henry

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\(^1\) M. L. Watson, "The Inheritance of Epilepsy and of Waltzing in Peromyscus," Contributions from the Laboratory of Vertebrate Genetics--University of Michigan, No. XI (July, 1939), 1.


\(^3\) J. R. Hamilton, "Epileptiform Convulsions in Rats. I. Description of the Phenomena and a Comparison with Symptomatology of Human Epilepsy," The Journal of Comparative Psychology, XXXIII (June, 1942), 297-303.

\(^4\) Letter from Dr. F. C. Coleman, Director, Department of Pathology, Mercy Hospital, Des Moines, Iowa, January 5, 1951.
state that, "no adequate explanation for the phenomenon has been advanced." These writers have attempted to outline the temporal course of physiological events leading to the development of an audiogenic seizure through electroencephalogram and electrocardiogram studies. It would appear, however, that delimitation of the precise mechanism involved will have to await further investigation.

In the present investigation the writer has attempted to pinpoint the mean age of death and the mean age of susceptibility to audiogenic seizures in an inbred strain of mice. An attempt was made to chart and to illustrate various aspects of seizure-behavior as age increases. Comparison was made between behavior observed during the orientation and stimulation periods as age increases. Such other factors as onset of susceptibility, latency of seizures, frequency of exposures, age at fatal seizure, frequency of seizures, number of seconds in fatal seizure, and age of onset of susceptibility within litters were investigated. In each case these factors were examined from the standpoint of increasing age, the assumption being that behavior increases, decreases, or changes as age increases.

The writer hopes that this investigation will point up valuable information and open up new avenues for investigation in this area.

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CHAPTER II

MATERIALS AND METHODS

The materials used in this investigation were those suggested by Scott.\(^1\) The bell-tub technique appears to be adequate to elicit the phenomenon.

The experiment was designed to include a standard galvanized tub, two No. 6 batteries, connecting wires, a jack-knife switch, a two and one-half inch doorbell, recording blanks, and a stop watch. The animals used were (dba) subline 2 stock raised by the writer in the Animal Room of the Fitch Pharmacy Building at Drake University. A total of seventy-five animals were used. These animals were from an original stock of twenty females and six males obtained from the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine. The animals were fed a diet of Pillsbury's Rabbit Pellets and water throughout the experiment. No attempt was made to separate the animals by sexes, for Mier and Glaser\(^2\) have found sex to be unrelated to susceptibility to audiogenic seizures.

Since the earliest age of onset of susceptibility was unknown,

\(^1\)Scott, op. cit., p. 583.

it was necessary to raise new experimental stock. These animals were housed by litter in separate cages throughout the experiment. At the time of the first stimulation each experimental animal was marked for identification within a litter.

Since it was known that the age of maximum frequency of audiogenic seizures in (dba) strains was around thirty days, the writer chose to begin stimulation at twenty days of age. It was found that a high percentage of fatal seizures occurred at this age. Since an age was desired at which virtually no symptomatic behavior would be elicited, the age was lowered to twelve days. This age was found to be satisfactory, since there was no evidence of response to auditory stimulation.

The experiment was designed to include two specific periods. The first period was designated the "orientation" or "adaptation" period and lasted for one minute. The second period was designated the "stimulation" period and lasted for two minutes. The orientation period gave the animal an opportunity to become familiar with the new surroundings before being subjected to stimulation.

The galvanized tub was placed on a solid surface with a 150 watt bulb directly above. This arrangement provided the interior of the tub with equal lighting. The bell was suspended from the inside of the tub and connected through a jack-knife switch with two No. 6 dry cell batteries.

When an animal reached twelve days of age, it was placed for the first time in the tub for a one-minute orientation period. Immediately following the orientation period, the switch was closed and the animal was stimulated for two minutes. Accurate timing was
accomplished by means of a stop watch. During both the orientation and the stimulation periods accurate records were made of various types of behavior. Each animal was stimulated once daily for two minutes until a fatal audiogenic seizure occurred.

The experiment was carried out in exactly the same manner for all seventy-five animals. The method for computing the mean and standard deviation of age of susceptibility and death was a short method described by Waugh.¹

CHAPTER III

EXPERIMENTAL RESULTS

Table 1 indicates the number of animals initially exhibiting seizure behavior at the various age levels. No animal responded to stimulation between ten and twelve days of age; fifty-six animals that had failed to respond abnormally at the earlier age gave the characteristic seizure pattern between thirteen and fifteen days. Eleven more animals became overtly susceptible between sixteen and eighteen days, and eight between nineteen and twenty-one days. It is evident that there is a continued and very appreciable decrease in the number of susceptible animals in the group up to eighteen days of age and that some animals gave initial evidence of their susceptibility as late as nineteen to twenty-three days of age.

Table 2 was reproduced from Finger's study on rats. This table indicates the number of animals initially exhibiting seizure behavior at the various age levels. These two tables appear to indicate that one of the determiners of susceptibility in rats and mice is age. The age range of thirteen to fifteen days in Table 1 appears to compare favorably with the age range of thirty-one to sixty days in Table 2.

1 Table 1, infra, p. 29.
2 Table 2, infra, p. 29.
Table 3\(^1\) indicates the age at which the greatest frequency of fatal seizures occurred. The greatest number of fatal seizures occurred at the age of sixteen to eighteen days. There seems to be a rapid decrease in mortality as age increases beyond this range.

Tables 1, 2, and 3\(^2\) appear to indicate that age is a determinant of susceptibility to audiogenic seizures. These tables indicate a very rapid increase in seizure behavior and fatal seizures as age increases. With further increment of age the behavior pattern seems to reach a point of maximum frequency, then decreases rapidly.

Table 4\(^3\) indicates the percentage of total behavior in the orientation period and Table 5\(^4\) the percentage of total behavior in the stimulation period. Both of these tables appear to indicate a general increase in the percentage of total behavior as age increases. At twelve days of age, in both the orientation and stimulation periods, total behavior was at a minimum, with the lowest percentages observed. At ages thirteen, fourteen, and fifteen days, the percentage of total behavior generally appears to increase. Beyond sixteen days there seems to be a general slowing up of total behavior.

It was observed that there is some variation in the percentage of behavior occurring as age increases. The details of the records

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\(^1\)Table 3, infra, p. 30.

\(^2\)Table 1, infra, p. 29; Table 2, infra, p. 29; Table 3, infra, p. 30.

\(^3\)Table 4, infra, p. 30.

\(^4\)Table 5, infra, p. 31.
indicate a lack of consistency between various types of behavior observed within a given period, but greater consistency for a given behavior as age increases. Apparently there is a continued and appreciable increase in the percent of a given behavior with increasing age. It appears that the general increase in percentage of behavior conforms with the trend of behavior observed in Tables 1, 2, and 3.  

Table 6 indicates the percentage of mortality as age increases. No animals were observed to suffer fatal seizures at twelve days of age. At thirteen to fifteen days, 17 percent suffered fatal seizures. The highest percentage of fatal seizures occurred at sixteen to eighteen days of age. Beyond eighteen days there appears to be a rapid decrease in the percent of fatal seizures.

Table 7 indicates the mean age of death and standard deviation of audiogenic seizures in (db)a subline 2 mice. When statistically calculated, the mean age of death is 18.68 days, with a standard deviation of 1.43. It would appear that the mean age of susceptibility would occur somewhat earlier.

Table 8 indicates the mean age and standard deviation of susceptibility to audiogenic seizures. The mean age of susceptibility to audiogenic seizures is 15.35 days, with a standard deviation of .998.

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1Table 1, infra, p. 29; Table 2, infra, p. 29; Table 3, infra, p. 30.
2Table 6, infra, p. 32.
3Table 7, infra, p. 33.
4Table 8, infra, p. 34.
The mean age of susceptibility appears to correspond with the age at which first symptoms of susceptibility appeared as demonstrated in Table 1. Since Table 3 indicates a very small number of fatal audiogenic seizures at thirteen to fifteen days, it might be expected that the mean age at which the animals become susceptible would be around fifteen days. It appears that the mean age of death closely follows the mean age of susceptibility.

It might be expected that the average time in a fatal audiogenic seizure would vary as age increases. The average number of seconds that an animal spends in a fatal seizure appears to have some significant variation as age increases. It seems that the animals spend considerably more time in fatal audiogenic seizures in the earlier and the later days of age. At fourteen days of age the average time in a fatal seizure was twenty seconds and at twenty-seven days of age the average time was twenty-five seconds. Between the ages of fifteen and twenty-two days there appears to be no significant variation in the average number of seconds the animals spend in fatal audiogenic seizures.

Since Table 1 indicated the age at which first symptoms of susceptibility appeared, it might be expected that the frequency of seizures would increase and decrease proportionately with age or would follow some other similar pattern. From thirteen to fifteen days of

1Table 1, infra, p. 29.
2Table 3, infra, p. 30.
3Table I, infra, p. 35.
4Table 1, infra, p. 29.
age there appears to be a rapid increase in the frequency of seizures, with a rapid decrease beyond sixteen days.\(^1\) It seems evident, therefore, that the increase is not proportionate to the decrease in the frequency of seizures nor does age systematically influence this factor.

It might be expected that the average age of onset of susceptibility to audiogenic seizures within litters would be quite consistent, since all animals were from the same stock and cared for under closely similar conditions. A total of sixteen litters with 4.7 animals per litter was used in this investigation. When the average age of onset of susceptibility within litters was determined, it was found that litters one to nine and thirteen to sixteen appeared to be quite consistent, while litters ten to twelve appeared to vary in consistency.\(^2\) The average age of onset of susceptibility to audiogenic seizures within litters was obtained by calculating the average age at which first seizures occurred for each increasing day of age.

The amount of time elapsing between the beginning of stimulation and the instant at which the animal goes into a violent convulsive seizure has been designated as the latency of audiogenic seizures. Since Table 1\(^3\) indicates that age may be a determiner of susceptibility to audiogenic seizures, it would appear that the latency of audiogenic seizures might increase as age increases. The details of the records revealed no evidence that the age factor systematically influenced the

\(^1\)Plate II, infra, p. 36.
\(^2\)Plate III, infra, p. 37.
\(^3\)Table 1, infra, p. 29.
average latency of audiogenic seizures.\textsuperscript{1} There appears to be no great variation in the latency from thirteen to twenty-two days of age, but there is a considerable increase from twenty-three to twenty-seven days. It seems, therefore, that considerable resistance to auditory stimulation occurs beyond twenty-five days of age. Since Table 7\textsuperscript{2} revealed that the mean age of death from auditory stimulation for (dba) subline 2 mice was around eighteen days, it might be expected that the latency of audiogenic seizures would increase rapidly beyond twenty days of age.

The average frequency of exposures per litter to auditory stimulation, prior to death, was calculated by taking the average of the number of exposures occurring within each litter. The details of the records revealed no evidence of consistency in the average number of exposures per litter prior to death.\textsuperscript{3} It appears, therefore, that little relationship exists between the average frequency of exposures per litter, prior to death, and the average age of onset of susceptibility within litters.\textsuperscript{4}

The frequency of exposures to auditory stimulation prior to susceptibility as age increases was calculated by summing the frequencies for the entire experimental stock for each increasing day of age.\textsuperscript{5} It will be noted that at twelve days of age each of the seventy-five animals was exposed to auditory stimulation without susceptibility without susceptibility

\begin{itemize}
\item \textsuperscript{1}Plate IV, infra, p. 38.
\item \textsuperscript{2}Table 7, infra, p. 33.
\item \textsuperscript{3}Plate V, infra, p. 39.
\item \textsuperscript{4}Plate III, infra, p. 37.
\item \textsuperscript{5}Plate VI, infra, p. 40.
\end{itemize}
being observed. From thirteen to fifteen days of age it appears that a very large percentage of the animals become susceptible to auditory stimulation. From sixteen to twenty days of age there seems to be a systematic decrease in the frequency of exposures prior to susceptibility. Beyond nineteen days of age susceptibility to auditory stimulation appears to occur with the first exposure.
CHAPTER IV

DISCUSSION

Since most of the information concerning behavior associated with age and audiogenic seizures appears to be from work done on rats, the conclusions that can be drawn concerning the reaction of mice must be with reference to them for comparison.

The literature indicates that the age factor may be important in the extent to which it may influence susceptibility to audiogenic seizures. From the standpoint of susceptibility and the influence of age, it appears that age may be highly significant as a determiner of susceptibility to audiogenic seizures, since the results of Finger's\(^1\) study and this investigation seem to be comparable. There seems to be evidence that at the early ages little, if any, symptomatic behavior is observed. As age increases, however, there appears to be a rapid increase in seizure behavior.\(^2\) With further increment of age there seems to be a gradual decrease in the symptoms of susceptibility to audiogenic seizures. The results seem clearly to indicate that one intrinsic determiner of susceptibility threshold is age.

The present data are in general agreement with the trend

\(^1\)Finger, "Factors Influencing Audiogenic Seizures in the Rat, II. Heredity and Age," op. cit., p. 230.

\(^2\)Table 1, infra, p. 29; Table 2, infra, p. 29.
reported by Mier and Glaser\(^1\) for studies on the rat, although the percentage of susceptible rats increases more slowly and for a longer period of time. The great age range over which first symptoms occur (from less than fourteen to more than twenty days) is perhaps surprising, but this dispersion emphasizes the fact that the age-susceptibility relationship is a highly individual matter and that only by repeated testing over a long period of time can the diagnosis of "susceptible" or "non-susceptible" be made with any degree of assurance. It is also evident that an animal once classified as "susceptible" may later fail to respond to auditory stimulation, simply as the result of changes associated with increased age. This failure to respond to auditory stimulation after susceptibility was established occurred very rarely in this investigation and may be attributed to the similarity of these animals. This appears to be confirmed by Fuller, who states that "inbreeding in the Jackson Memorial Laboratory strains of mice has reduced individual genetic variability to the lowest possible amount."\(^2\)

The conviction that susceptibility to auditory stimulation is largely controlled by age appears to be confirmed by the age at which fatal audiogenic seizures occurred.\(^3\) Since the greatest frequency of fatal seizures occurred between sixteen and eighteen days of age, it may be assumed that susceptibility occurs at an earlier age.\(^4\)

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\(^1\)Mier and Glaser, *op. cit.*, pp. 24-25.

\(^2\)Letter from J. L. Fuller, Division of Behavior Studies, Jackson Memorial Laboratory, Bar Harbor, Maine, April 6, 1950.

\(^3\)Table 3, *infra*, p. 30.

\(^4\)Plate I, *infra*, p. 35.
Fuller\(^1\) has indicated that in the (dba) strains there is a gradual onset of susceptibility beginning at about twenty days, reaching a peak from thirty to forty days, declining to sixty days, and declining fairly rapidly after sixty days of age.

The results of this investigation seem to indicate that the onset of susceptibility for (dba) subline 2 mice occurs at an earlier age. It was also found that the peak of susceptibility occurred at an earlier age. This investigation also seems to indicate that the age at which susceptibility declines is somewhat earlier.

There may be several reasons why such a variation appears to exist between the results of this investigation and those stated by Fuller. Since Fuller's statement seems to cover all (dba) strains, it may be assumed that subline 2 stock used in this investigation may vary in their susceptibility from that found for all (dba) strains. This variation may also be attributed to the influence of nutritional factors.

The animals at Jackson Memorial Laboratory were raised on Purina Laboratory Chow and those in this investigation on Pillsbury Rabbit Pellets. Patton, Karn, and King\(^2\) indicate that nutritional factors are important determiners of seizure susceptibility. They have indicated that the high incidence of seizures could be markedly reduced in rats by providing a vitamin B\(_1\) supplement to the original diet. Since Pillsbury Pellets contain only small amounts of vitamin B\(_1\), it may be assumed that

\(^{1}\text{Letter from J. L. Fuller, Division of Behavior Studies, Jackson Memorial Laboratory, Bar Harbor, Maine, February 7, 1950.}\)

\(^{2}\text{R. A. Patton, H. W. Karn, and C. G. King, "Studies on the Nutritional Basis of Abnormal Behavior in Albino Rats, II. Further Analysis of the Effects of Inanition and Vitamin B\(_1\) on Convulsive Seizures," The Journal of Comparative Psychology, XXXIII (April, 1942), 257.}\)
this contributed, in part, to the early susceptibility of the animals.

In this investigation no attempt was made to control sex since Mier and Glaser\textsuperscript{1} indicate that susceptibility is not influenced by sex.

The term "behavior" as used in this investigation is defined as any observable physical reaction to stimulation. This behavior is characterized by violent running, jumping, and stiff-hopping movements. The animal may dash rapidly across the tub, circle the inside of the tub, jump up on the walls, or attempt to climb the walls of the tub. The animal may groom itself, freeze in one position, urinate and defecate. This latter behavior is usually followed by an audiogenic seizure.

The age factor appears to have a significant bearing on the behavior observed throughout this investigation. The behavior seems to increase in both the orientation and stimulation periods.\textsuperscript{2} In both periods there was evidence of a general increase in the percent of behavior as age increases. In the earlier days of age behavior seems to be at a minimum, with a general increase occurring as age increases.

In this investigation the period of greatest mortality, considering all ages, was between sixteen and eighteen days.\textsuperscript{3} There are several individuals scattered above and below this period which might be explained by assuming that individual differences may have some effect. Since all animals suffered fatal audiogenic seizures, it may be assumed that there is some variation in maturation.

\begin{itemize}
\item \textsuperscript{1}Mier and Glaser, \textit{op. cit.}, p. 27.
\item \textsuperscript{2}Table 4, \textit{infra}, p. 30; Table 5, \textit{infra}, p. 31.
\item \textsuperscript{3}Table 6, \textit{infra}, p. 32.
\end{itemize}
This investigation revealed that with repeated testing susceptibility may be reduced. This was observed to occur beyond twenty-two days of age and was characterized by behavior of an adaptive nature. This behavior consisted of freezing in one position with the animal's back toward the source of the stimulus and slow, deliberate movements, usually away from the stimulus.

Since there is some evidence that repeated testing may reduce susceptibility, the animals that lived from twenty-two to twenty-seven days of age may have adapted themselves to the stimulation. This number is very small, however, when compared with those who suffered fatal audiogenic seizures at an earlier age.

The details of the records, thus far, appear to indicate that age exerts a decided influence on behavior and susceptibility to audiogenic seizures.

The literature on audiogenic seizures has offered no evidence concerning the mean age of death and the mean age of susceptibility to audiogenic seizures. Since the purpose of this investigation was to study the behavior associated with age, it was felt that such information would be of value. It was found that the mean age of death occurred at about 18.68 days and the mean age of susceptibility at about 15.35 days.\(^1\) The determination of these two means may assist other investigators in pinpointing the minimum and maximum ages at which susceptibility and death might be expected to occur for (dba) subline 2 mice.

The margin of difference between these two means seems to be

\(^1\)Table 7, infra, p. 33; Table 8, infra, p. 34.
quite small. It may be assumed, therefore, that a rapid increase in susceptibility occurs as age increases with the maximum age of susceptibility following closely. This observation appears to show no departure from previous observations made in this investigation.

Inasmuch as the age factor seems to be quite important in audiogenic seizures, it might be assumed that the frequency of audiogenic seizures would follow the same general pattern as suggested earlier. It was indicated that, as age increases, behavior increases rapidly up to a certain age, then falls off rapidly. The details of the records indicate no significant departure from previous observations. At the earlier ages it was observed that the frequency of audiogenic seizures was very slight and that with increasing age the frequency of seizures increased rapidly. Beyond the age at which seizures occurred most frequently, there is a decided decrease, with a more gradual decrease as age increases.

As suggested earlier, some animals appeared to adapt or adjust to the stimulation. This was observed in a small number of animals. Although adaptation was observed in some animals, all animals suffered fatal audiogenic seizures prior to thirty days of age. Further investigation of adaptation may be necessary before any conclusion concerning its influence on audiogenic seizures may be made.

Since there seems to be a fairly consistent pattern of behavior in audiogenic seizures, it might be assumed that other factors associated with age would follow this pattern. Inasmuch as each animal was stimulated under identical conditions, it would seem that each animal

\[\text{Plate II, infra, p. 36.}\]
might spend approximately the same number of seconds in a fatal seizure.\(^1\)
The details of the records, however, do not seem to bear out this hypothesis. There appears to be no positive relationship between increasing age and the number of seconds an animal may remain in a fatal audiogenic seizure. The average number of seconds in a fatal seizure seems to vary considerably with age. This variation may be explained by adaptation and individual differences in maturation and in susceptibility. To measure the average number of seconds in a fatal seizure for a large number of animals, many factors would have to be carefully controlled. This would seem to necessitate further investigation.

Literature was cited which indicated that little variation existed between animals of the same subline. It would seem, therefore, that little variation would exist between litters of the same subline.

When the average age of onset of susceptibility to audiogenic seizures within litters was determined, it was found that considerable consistency existed.\(^2\) The details of the records indicate that the average age of onset of susceptibility for each litter occurs between fourteen and sixteen days of age. In only three litters was an exception noted. The average age of susceptibility for litters one, ten, and eleven occurred at thirteen and one-half, nineteen, and eighteen and one-half days, respectively. The variation of these three litters is difficult to account for, but may be attributed to the age of the parent at conception and to intra-uterine development. No attempt was made to investigate these factors. The evidence of the records appears to indicate considerable consistency

\(^1\)Plate I, infra, p. 35.

\(^2\)Plate III, infra, p. 37.
between litters of the same subline when subjected to auditory stimulation.

The latency of audiogenic seizures has been defined as the amount of time elapsing between the beginning of stimulation and the instant at which the animal goes into a violent convulsive seizure. In this investigation the average latency of audiogenic seizures as age increases was determined.\(^1\) The details of the records revealed no evidence that the age factor systematically influenced the average latency of audiogenic seizures. There appears to be evidence of considerable increase in average latency at twenty-three, twenty-four, and twenty-seven days of age. For those animals who did not suffer fatal audiogenic seizures before twenty-three days of age, considerable stimulus resistance was observed. This resistance may have been due to physiological changes in the animal or to adaptation to the stimulus. In general the average latency does not seem to vary to any great extent between thirteen and twenty-two days of age.

No consideration was given to sex and its relation to latency, for Morgan\(^2\) has indicated that there is no difference in latency with respect to sex.

An attempt was made to compare the average frequency of exposures to auditory stimulation for May and June litters, prior to fatal audiogenic seizures.\(^3\) This portion of the investigation was carried out in order to determine if any significant variation in the

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\(^1\)Plate III, infra, p. 37.
\(^2\)Morgan, op. cit., p. 278.
\(^3\)Plate V, infra, p. 39.
average number of exposures could be observed as the age of the producing animals increased.

The details of the records fail to indicate any significant variation between litters born in May and June, even though the age of the producing animals had increased. Fifth and sixth litters from the same female were not used in the experimental group.

The final step in this investigation concerned the frequency of exposures to auditory stimulation as age increased prior to susceptibility.¹ As previously indicated, no animal became susceptible at twelve days of age, thus seventy-five exposures were necessary at this age. The details of the records indicate that the frequency of exposures prior to susceptibility decreases rapidly to around fifteen days of age. From this point on the decrease is more gradual, indicating that the mean age of susceptibility has been passed.

The age factor again appears to be an important determiner of behavior and susceptibility to audiogenic seizures in (dba) subline 2 mice.

¹Plate VI, infra, p. 40.
CHAPTER V

SUMMARY AND CONCLUSIONS

Dilute Brown non-agouti (dba) subline 2 mice were used in this investigation. A total of seventy-five mice were tested for susceptibility to audiogenic seizures beginning at twelve days of age and continuing until all animals had suffered fatal seizures. During the course of this investigation consideration was given to behavior associated with age and audiogenic seizures.

Ten mice were mated. The seventy-five offspring in the sixteen litters were tested with the same intense auditory stimulation under identical conditions.

1. In the offspring it was demonstrated that the age at which first symptoms of susceptibility to audiogenic seizures occurred was between thirteen and fifteen days.

2. It was demonstrated that the age at which fatal audiogenic seizures occurred was between sixteen and eighteen days.

3. It was demonstrated that the percentage of behavior observed as age increases, during the orientation and stimulation periods tends to increase. This behavior was characterized by violent running, jumping, and stiff-hopping movements; crossing the diameter of the tub, circling the inside of the tub, jumping, and climbing on the walls of the tub. The animals were also observed to groom themselves, freeze in one position, urinate, and defecate. This latter behavior was usually followed by an audiogenic seizure.

4. The percent mortality resulting from audiogenic seizures as age increases was demonstrated to be greatest between sixteen and eighteen days.
5. The mean age of susceptibility and death were determined. In some mice the increase of age beyond a certain point was accompanied by a decline in susceptibility, although all animals suffered fatal seizures prior to thirty days of age.

6. The average number of seconds in a fatal seizure was determined. In a few animals the increase of age beyond a certain point was accompanied by behavior which appeared adaptive in nature.

7. It was demonstrated that the frequency of audiogenic seizures as age increases was greatest between fourteen and sixteen days.

8. The average age of onset of susceptibility within litters was found to occur between fourteen and sixteen days.

9. It was found that no systematic increase occurred in the average latency of audiogenic seizures as age increases. Increase at the later ages may be attributed to maturation and adaptation.

10. It was demonstrated that little difference exists between the average frequency of exposures to auditory stimulation for May and June litters.

11. It was found that the frequency of exposures to auditory stimulation as age increases prior to susceptibility, decreases rapidly from twelve to fifteen days of age and more gradually thereafter.

12. When a comparison was made between the results of this investigation and those reported in Finger's study, no significant variation appeared to exist.

This investigation has attempted to explore a number of behavior factors associated with age and audiogenic seizures in an inbred strain of mice. The results of this investigation appear to indicate that age influences behavior and determines susceptibility to audiogenic seizures in (dba) subline 2 mice.

APPENDIX
### Table 1

**The Age at Which First Symptoms of Susceptibility to Audiogenic Seizures Occurred in 75 (DBA) Subline 2 Mice**

<table>
<thead>
<tr>
<th>Age Range in Days</th>
<th>Number of First Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 12</td>
<td>0</td>
</tr>
<tr>
<td>13 - 15</td>
<td>56</td>
</tr>
<tr>
<td>16 - 18</td>
<td>11</td>
</tr>
<tr>
<td>19 - 21</td>
<td>8</td>
</tr>
<tr>
<td>22 - 24</td>
<td>0</td>
</tr>
<tr>
<td>25 - 27</td>
<td>0</td>
</tr>
<tr>
<td>28 - 30</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2

**The Age at Which First Symptoms of Susceptibility to Audiogenic Seizures Appeared**

<table>
<thead>
<tr>
<th>Age Range in Days</th>
<th>Number of First Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 30</td>
<td>7</td>
</tr>
<tr>
<td>31 - 60</td>
<td>36</td>
</tr>
<tr>
<td>61 - 90</td>
<td>12</td>
</tr>
<tr>
<td>91 - 120</td>
<td>19</td>
</tr>
<tr>
<td>121 - 150</td>
<td>13</td>
</tr>
<tr>
<td>151 - 180</td>
<td>3</td>
</tr>
<tr>
<td>181 - 210</td>
<td>1</td>
</tr>
<tr>
<td>211 - 240</td>
<td>6</td>
</tr>
<tr>
<td>241 - 270</td>
<td>2</td>
</tr>
</tbody>
</table>

### TABLE 3

<table>
<thead>
<tr>
<th>Age Range in Days</th>
<th>Number of Fatal Seizures</th>
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</thead>
<tbody>
<tr>
<td>10 - 12</td>
<td>0</td>
</tr>
<tr>
<td>13 - 15</td>
<td>13</td>
</tr>
<tr>
<td>16 - 18</td>
<td>36</td>
</tr>
<tr>
<td>19 - 21</td>
<td>19</td>
</tr>
<tr>
<td>22 - 24</td>
<td>6</td>
</tr>
<tr>
<td>25 - 27</td>
<td>1</td>
</tr>
<tr>
<td>28 - 30</td>
<td>0</td>
</tr>
</tbody>
</table>

### TABLE 4

<table>
<thead>
<tr>
<th>Days of Age</th>
<th>Crossing Tub</th>
<th>Circling Tub</th>
<th>Wall Jumping</th>
<th>Wall Climbing</th>
<th>Grooming</th>
<th>Urination</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>26</td>
<td>5</td>
<td>0</td>
<td>13</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>40</td>
<td>9</td>
<td>4</td>
<td>24</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>29</td>
<td>5</td>
<td>1</td>
<td>12</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>9</td>
<td>0</td>
<td>16</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>34</td>
<td>14</td>
<td>6</td>
<td>21</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>43</td>
<td>23</td>
<td>14</td>
<td>34</td>
<td>32</td>
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<td>18</td>
<td>42</td>
<td>6</td>
<td>3</td>
<td>27</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>48</td>
<td>22</td>
<td>4</td>
<td>22</td>
<td>32</td>
<td>0</td>
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<tr>
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<td>47</td>
<td>28</td>
<td>5</td>
<td>14</td>
<td>32</td>
<td>0</td>
</tr>
</tbody>
</table>
### TABLE 5

PERCENT BEHAVIOR OBSERVED DURING TWO-MINUTE STIMULATION PERIOD AS AGE INCREASES FOR 75 (DBA) SUBLINE 2 MICE

<table>
<thead>
<tr>
<th>Days of Age</th>
<th>Grooming</th>
<th>Wall Jumping</th>
<th>Circling Tub</th>
<th>Crossing Tub</th>
<th>Urination</th>
<th>Wall Climbing</th>
<th>Non-Fatal Seizure</th>
<th>Fatal Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>36</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>13</td>
<td>18</td>
<td>13</td>
<td>10</td>
<td>6</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>38</td>
<td>34</td>
<td>45</td>
<td>24</td>
<td>32</td>
<td>18</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>48</td>
<td>67</td>
<td>35</td>
<td>59</td>
<td>12</td>
<td>64</td>
<td>7</td>
</tr>
<tr>
<td>16</td>
<td>27</td>
<td>56</td>
<td>75</td>
<td>39</td>
<td>56</td>
<td>9</td>
<td>72</td>
<td>39</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>49</td>
<td>62</td>
<td>34</td>
<td>34</td>
<td>15</td>
<td>51</td>
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<td>18</td>
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<td>64</td>
<td>33</td>
<td>41</td>
<td>33</td>
<td>53</td>
<td>28</td>
</tr>
<tr>
<td>19</td>
<td>31</td>
<td>66</td>
<td>77</td>
<td>46</td>
<td>46</td>
<td>19</td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>60</td>
<td>80</td>
<td>45</td>
<td>55</td>
<td>5</td>
<td>55</td>
<td>30</td>
</tr>
</tbody>
</table>
TABLE 6
PERCENT MORTALITY RESULTING FROM AUDIODOGENIC SEIZURES AS AGE INCREASES FOR 75 (DBA) SUBLINE 2 MICE

<table>
<thead>
<tr>
<th>Age Range in Days</th>
<th>Percent Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 12</td>
<td>0</td>
</tr>
<tr>
<td>13 - 15</td>
<td>17</td>
</tr>
<tr>
<td>16 - 18</td>
<td>48</td>
</tr>
<tr>
<td>19 - 21</td>
<td>26</td>
</tr>
<tr>
<td>22 - 24</td>
<td>8</td>
</tr>
<tr>
<td>25 - 27</td>
<td>1</td>
</tr>
<tr>
<td>28 - 30</td>
<td>0</td>
</tr>
</tbody>
</table>
TABLE 7
MEAN AGE OF DEATH AND STANDARD DEVIATION OF AUDIOGENIC SEIZURES FOR 75 (DBA) SUBLINE 2 MICE

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Frequency</th>
<th>Deviation</th>
<th>Frequency Deviation</th>
<th>Frequency Deviation^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 31</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>28 - 29</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>26 - 27</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>24 - 25</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>22 - 23</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>20 - 21</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18 - 19</td>
<td>13</td>
<td>-1</td>
<td>-13</td>
<td>13</td>
</tr>
<tr>
<td>16 - 17</td>
<td>28</td>
<td>-2</td>
<td>-56</td>
<td>112</td>
</tr>
<tr>
<td>14 - 15</td>
<td>13</td>
<td>-3</td>
<td>-39</td>
<td>117</td>
</tr>
<tr>
<td>12 - 13</td>
<td>1</td>
<td>-4</td>
<td>-4</td>
<td>16</td>
</tr>
<tr>
<td>10 - 11</td>
<td>0</td>
<td>-5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>fd -99</td>
<td>fd^2 285</td>
<td></td>
</tr>
</tbody>
</table>

\[
\bar{x} = \bar{x} + c \left( \frac{\sum fd}{\sum f} \right) \\
\sigma = c i \sqrt{\frac{\sum (fd)^2}{N}} - \left( \frac{\sum fd}{N} \right)^2
\]

\[
\bar{x} = 18.68 \\
\sigma = 1.43
\]

\(\bar{x}\) - Mean

\(\sigma\) - Standard Deviation
### TABLE 8

**MEAN AGE OF SUSCEPTIBILITY AND STANDARD DEVIATION OF AUDIOGENIC SEIZURES FOR 75 (DBA) SUBLINE 2 MICE**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Frequency</th>
<th>Deviation</th>
<th>Frequency Deviation</th>
<th>Frequency Deviation^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 - 23</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 - 21</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>18 - 19</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>16 - 17</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14 - 15</td>
<td>47</td>
<td>-1</td>
<td>-47</td>
<td>47</td>
</tr>
<tr>
<td>12 - 13</td>
<td>9</td>
<td>-2</td>
<td>-18</td>
<td>36</td>
</tr>
<tr>
<td>10 - 11</td>
<td>0</td>
<td>-3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>N-Total</strong></td>
<td><strong>75</strong></td>
<td></td>
<td><strong>fd -49</strong></td>
<td><strong>fd^2 107</strong></td>
</tr>
</tbody>
</table>

\[ \bar{x} = \bar{x} + C1 \left( \frac{\Sigma fd}{\Sigma f} \right) \]

\[ \sigma = C1 \sqrt{\frac{\Sigma (fd^2)}{N} - \left( \frac{\Sigma fd}{N} \right)^2} \]

\[ \bar{x} = 15.35 \]

\[ \sigma = .998 \]

\( \bar{x} \) - Mean

\( \sigma \) - Standard Deviation
PLATE I

THE AVERAGE NUMBER OF SECONDS IN A FATAL AUDIOGENIC SEIZURE AS AGE INCREASES FOR 75 (DBA) SUBLINE 2 MICE

*Number of Animals at Each Day of Age
PLATE II

THE FREQUENCY OF AUDIgenic SEIZURES AS AGE INCREASES FOR 75 (DBA) SUBLINE 2 MICE

![Graph showing the frequency of audiogenic seizures as age increases for 75 (DBA) subline 2 mice.](image-url)
PLATE III

THE AVERAGE AGE OF ONSET OF SUSCEPTIBILITY TO AUDIOGENIC SEIZURES WITHIN LITTERS FOR 75 (DBA) SUBLINE 2 MICE
PLATE IV

THE AVERAGE LATENCY OF AUDIOGENIC SEIZURES AS AGE INCREASES FOR 75 (DBA) SUBLINE 2 MICE

Days

Time in Seconds

Age of Animals at Time of Stimulation
PLATE V

THE AVERAGE FREQUENCY OF EXPOSURES TO AUDITORY STIMULATION FOR MAY AND JUNE LITTERS PRIOR TO FATAL AUDIOGENIC SEIZURES FOR 75 (DBA) SUBLINE 2 MICE
PLATE VI

THE FREQUENCY OF EXPOSURES TO AUDITORY STIMULATION AS AGE INCREASES PRIOR TO SUSCEPTIBILITY FOR 75 (DBA) SUBLINE 2 MICE
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