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Sound-Induced Seizures in Rats Reared on Diets with High Sugar Content

Lois L. Benedict

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SOUND-INDUCED SEIZURES IN RATS REARED ON DIETS WITH HIGH SUGAR CONTENT

A Thesis
Presented to
the Faculty of the Department of Psychology
The University of New Mexico

In Partial Fulfillment
of the Requirements for the Degree
Master of Science

by
Lois L. Benedict
June 1951

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MASTER OF SCIENCE

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DATE

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INTRODUCTION

Carbohydrate metabolism is a complex process about which uncertainties still exist. Biologists in general believe, and most textbooks state, that most or all carbohydrates taken into the body are converted to glucose or glycogen before they are utilized. This point of view is not unreasonable since transformations of one sugar into another are common in experiments _in vitro_.[1] Upon hydrolysis, glycogen yields glucose as the chief and probably the only product, so it should be of little consequence if sugars such as fructose and galactose are converted first into glucose or if they are directly synthesized into glycogen. However, the glycogen formed from galactose may be chemically different from that resulting from glucose; one study observed that glycogen after galactose feeding is built of eighteen hexose units rather than the twelve units found after glucose feeding.[2] It has also been observed that the glycogen originating from galactose is more stable than that formed from other materials, and that it may perhaps be more

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[1] Benjamin Harrow, _Textbook of Biochemistry_ (Philadelphia: W. B. Saunders Company, 1944), p. 306.

[2] Philip Handler, "The Biochemical Defect Underlying the Nutritional Failure of Young Rats on Diets Containing Excessive Quantities of Lactose or Galactose," _Journal of Nutrition_, 33: 231, 1947.

beneficial to the organism.[3] The significance of these observations has not been determined.

According to this commonly accepted belief, the particular digestible carbohydrate included in the diet is of little importance; "the normal sugar of circulating blood is glucose, quite irrespective of the carbohydrate material at the time of absorption."[4] On the other hand, several authors, (*e.g.*, Mitchell,[5] Gortner,[6] Mathews[7]), while accepting this theory, mention the possible importance of lactose, the sugar of milk, for the growth of brain and nerve tissue containing galactose. One author, assuming an extreme viewpoint, states:

> The relation of lactose to brain size . . . may be explained by the fact that on hydrolysis lactose yields one molecule of galactose as well as one of glucose. The brain is rich in galactosides, that is, substances which contain galactose (as well as fatty acids and nitrogenous substances). It is reasonable to assume that the larger the brain and the more rapid its early growth, the more

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[3] Samuel Soskin and Rachmiel Levine, *Carbohydrate Metabolism* (Chicago: University of Chicago Press, 1946), p. 22.

[4] Benjamin Harrow, *loc. cit.*

[5] Philip H. Mitchell, *A Textbook of Biochemistry* (New York: McGraw-Hill Book Company, Inc., 1946), p. 380.

[6] Ross A. Gortner, *Outlines of Biochemistry* (New York: John Wiley and Sons, Inc., 1929), p. 544.

[7] A. P. Mathews, *Physiological Chemistry* (New York: William Wood and Company, 1930), p. 318.

> galactose it needs for its galactosides, and therefore the more lactose it needs in the diet; and that different species of mammals developed milks with lactose levels in proportion to their needs for galactose.
>
> Glucose could, theoretically, be used in place of galactose for the production of brain and nerve tissue; practically, however, glucose may not be stable enough; it is too readily oxidized, indeed, glucose is apparently the only fuel normally oxidized by the brain. Galactose, a more stable sugar, was therefore presumably evolved. The consumption of galactose in the form of lactose thus increases the stability of the brain and nervous system above what it would be if glucose were the only available sugar. The adult may be able to synthesize the galactose to supply the normal metabolic needs of the nervous system, but the infant may not be able to synthesize the lactose at a sufficiently rapid rate during early rapid growth and development. But even the adult's nervous sytem may, perhaps, benefit, perhaps maintain higher stability, by consuming lactose. . . .
>
> There is no experimental evidence for the suggestion that lactose may serve as a "stabilizer" for the nervous system, but it is not unreasonable. It is known that the tetany following parathyroidectomy may be prevented or stopped by a milk diet. This effect is attributed to the calcium in the milk and to the antirachitic effect of the lactose. . . . But it is also possible that the lactose itself may also have a stabilizing effect on the nervous system by supplying it with the "building-stone" galactose.[8]

The comparison of the evolutionary increase in the ratio of brain weight to body weight and the increase in the proportion of lactose in milk is an interesting one.

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[8] S. Brody and D. P. Sadhu, "The Nutritional Significance of Milk With Special Reference to Milk Sugar," The Nutritional Value of the Non-Fat Milk Solids (Chicago: Cherry-Burrell Corp., 1947), pp. 16-17, cited by N. R. F. Maier and Joan U. Longhurst, "The Effect of a Lactose-Free Diet on Problem Solving Behavior in Rats," Journal of Comparative and Physiological Psychology, 43: 375-376, 1950.

According to the theory so far outlined, however, this comparison is meaningless; if all carbohydrates are converted to glucose before being utilized by the body, of what significance is the presence of lactose or galactose in milk?

The origin of galactose used for the development of galactosides (also called cerebrosides or galacto-lipids) has not been described except by means similar to that cited above. It is known that the mammary glands are capable of synthesizing galactose from glucose for the production of lactose; except for these glands, animal organs appear to be unable to form galactose.[9] It is also known that the mammary glands of infants are functional, and it is possible that these may supply galactose to be transported to the brain and nervous system.

In contrast to the widely accepted belief is this recent evidence: excessive galactose or lactose in the diet appears to produce effects in the organism different from those produced by excessive amounts of other sugars, including glucose. Differences have been observed by several investigators, and some of the experimental results will be presented in a section which follows. If these results are valid, the suggestions offered by Brody and Sadhu (Supra) and others are possible, and further experimentation is

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[9] Philip H. Mitchell, *loc. cit.*

desirable. Investigations up to this time have been chiefly concerned with the health and growth of animals, but it is conceivable that lactose and galactose might also influence behavior through the nervous system. Psychological measurements would seem a necessary contribution to the greater understanding of the possible differential effects of these carbohydrates.

In summary, the possibilities of the fate of galactose in the body are as follows:

(1) Galactose may be converted to glucose, or it may be synthesized into glycogen which upon hydrolysis forms glucose.

(2) Part of the galactose may be changed to glucose or glycogen, and part may empty into the general circulation unchanged. If this is true, the galactose in the blood may be excreted in the urine without producing any effect in the body, or it may enter body tissues.

Differing opinions on these possibilities indicate that it is difficult to determine what happens to the normal amount of galactose absorbed into the body. Hence, a logical approach is to include abnormal amounts of lactose, galactose, and other sugars in the diet in order to attempt to trace their comparative effects. If successful results are obtained from investigations of this type, determination of the effects of normal intake of lactose or galactose might

be made easier.

The most common, and perhaps the only source of galactose for the mammalian body is lactose, a sugar peculiar to milk and not found in body tissues other than the mammary glands. Since milk and milk products are very important from a nutritional standpoint, it seemed desirable to investigate lactose rather than galactose alone. The functions of glucose in the body are well enough known that it would seem reasonable to attribute any changes in behavior to the galactose molecule.

The present study was not designed to investigate the controversy on carbohydrate metabolism. For experimental purposes, the second possibility mentioned above was assumed to be true, *i.e.*, that, somehow, ingested galactose might possibly be transported through the circulatory system. As long as this theory remains tenable, experimentation based upon it is necessary.

THE PROBLEM

Statement of the problem. The purpose of this experiment was to investigate the effect of increased lactose in the diet on the incidence of sound-induced seizures in rats. This effect was compared with those of an increased dextrose, or glucose, diet and a diet with no added sugar. A factorial design was employed whereby the parental background and the age at which the animals were tested were also varied.

Importance of the study. This problem attempts to contribute to the better understanding of lactose and its possible influence on behavior. Also, a multitude of factors have been found to influence the incidence of convulsive seizures. The work in this field has been reviewed by Finger, who states that further investigation of the effects of nutritional factors "gives promise of yielding results of broad significance".[10] If lactose were found to influence sound-induced seizures, some knowledge might be added to the extensive investigations of convulsive behavior.

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[10] Frank W. Finger, "Convulsive Behavior in the Rat," Psychological Bulletin, 44: 229, 1947.

REVIEW OF THE LITERATURE

Literature on lactose. As has been stated, most experiments involving lactose or galactose employ physical measurements only. Handler[11] determined that young rats fed diets in which lactose or galactose was the sole carbohydrate failed to grow properly and died within three to seventeen days. The percentages of carbohydrate in the diets were varied for different experimental groups, and the remainder of the ration consisted of casein, salts, cod liver oil, cottonseed oil, corn oil, and small amounts of thiamine, riboflavin, pyridoxine, calcium pantothenate, nicotinic acid, choline chloride, inositoe, p-aminobenzoic acid, mixed tocopherols, and napthohydroquinone acetate. The diets which were inadequate for health and growth contained 40 per cent or more galactose or 60 per cent or more lactose; a diet containing galactose and glucose produced similar effects, while glucose alone did not, indicating that the galactose portion of lactose was the injurious one. Most rats on diets including lactose showed at least moderate diarrhea, as did some on diets including galactose; this could not be effectively controlled by the administration of cellulose or sulfasuxidine. Thorough examination of the animals revealed

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[11] Philip Handler, op. cit., pp. 221-233.

that the feeding of lactose and galactose consistently resulted in a lowering of the blood glucose, the serum phosphorus, and the liver glycogen; lactose feeding also increased the serum calcium. Urinalysis showed excretion of galactose, but "in no case was the sugar excretion of sufficient magnitude to impose a serious caloric want".[12] Complete autopsies of lactose-fed and galactose-fed rats found nothing which seemed contributory to an understanding of the nutritional failure. The author concludes that death was due to no specific factor but to a fundamental disturbance of carbohydrate metabolism. The means by which the sugars interfered with metabolism could not be clearly defined.

Other investigators found that an otherwise complete diet containing 35 per cent galactose produced cataracts in their rats in an average of 5.8 days.[13] Ershoff[14] has reported that animals fed only lactose or galactose, by the single-food choice method, did not survive significantly longer than rats fed no food at all; the development of

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[12] Ibid., p. 225.

[13] William J. Darby and Paul L. Day, "Blood Sugar Levels in Rats Receiving the Cataractogenic Sugars Galactose and Xylose," Journal of Biological Chemistry, 133: 508, 1940.

[14] Benjamin H. Ershoff, "Studies on the Nutritive Value of Lactose and Galactose with the Single-Food Choice Method," American Journal of Physiology, 147: 13-18, 1946.

diarrhea and cataracts was also reported. However, the results differed from those of Handler in that length of survival on diets of 50 per cent galactose and 50 per cent dextrose, or 70 per cent galactose and 30 per cent butter-fat, was approximately the same as that on diets of only dextrose, sucrose, or butter-fat, which are adequate for growth. On these combined diets, the animals increased their food consumption and water intake to an extent great enough to indicate that sufficient calories were being obtained from the dextrose or butter-fat, while the galactose was excreted in the urine. An unexpected finding was the development of severe flaccid paralysis in the dextrose-galactose and butter-fat-galactose groups, which appeared in about twenty-six days. Since rats on only dextrose or butter-fat did not develop paralysis, galactose would appear to be responsible; animals fed only lactose or galactose in this study died within five to seven days, and no indication of the paralysis appeared before the sixteenth day on the experimental diet.

Another study[15] found slow growth, poor appetites, and diarrhea in animals on diets containing as high as 60 per cent lactose. Other components of these diets were dried

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[15] H. H. Mitchell, T. S. Hamilton, and J. R. Beadles, "The Comparative Nutritive Values of Glucose, Fructose, Sucrose, and Lactose When Incorporated in a Complete Diet," Journal of Nutrition, 14: 435-452, 1937.

whole egg (25 per cent), agar, cod liver oil, yeast, and salt mixture. The rate of growth for lactose-fed rats was only 60 per cent of that of glucose-fed rats; only one rat of the group maintained on lactose died before the end of the experiment. Examination of the carcass composition of lactose-fed rats showed more water, less fat and protein, and more ash, calcium, and phosphorus than found in animals maintained on glucose.

In spite of the effects produced by diets containing large amounts of lactose or galactose, smaller quantities appear to be nutritionally adequate. When fed at moderate levels of no more than 20 to 25 per cent of a complete diet, lactose was found to be comparable to sucrose in growth-promoting value. No significant superiority for either sugar appeared, and both proved to be comparable to starch.[16]

In the psychological field, Maier and Longhurst have made a series of studies concerning the effects of a lactose-free diet on the behavior of rats; the first of this series was published recently.[17] In this, a lactose-free diet and a diet containing 10 per cent lactose were compared for their

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[16] Julia Outhouse and others, "A Comparative Study of the Growth-Promoting and Bone-Calcifying Effects of Several Carbohydrates," Journal of Nutrition, 14: 587, 1937.

[17] N. R. F. Maier and Joan U. Longhurst, *op. cit.*, pp. 375-388.

influences upon higher mental processes, i.e., reasoning. The results reveal that three of four groups reared on the lactose-free diet were significantly inferior in reasoning scores than the groups whose diet included lactose. An interesting observation to be added to the list of biological influences was that females who were of a second generation maintained on a lactose-free diet were unable to nurse their young; although the litters were normal-appearing at birth, all died of apparent starvation within a few days.

Though no experiment was conducted, Patton observed that audiogenic seizures could be induced in lactating females who had never before exhibited this behavior.[18] If it were found that the absence of galactose increased susceptibility to seizures, or that an increase in galactose reduced susceptibility, it would seem reasonable that the production of milk consumed galactose normally utilized in other parts of the body. An experimental investigation of this factor might provide interesting results.

Literature on seizures. All experiments on convulsive behavior have been recently reviewed by Finger.[19] Of the many variables influencing abnormal behavior, the present study

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[18] Robert A. Patton, "The Effect of Vitamins on Convulsive Seizures in Rats Subjected to Auditory Stimulation," Journal of Comparative Psychology, 31: 215-221, 1941.

[19] Frank W. Finger, op. cit., pp. 201-248.

was concerned with only three: differences in age, genetic background, and diet. The experiment was not designed to study thoroughly the effects of age or genetic background, but these variables were systematically varied rather than held constant.

Maier and Glaser[20] have shown that the susceptibility to seizures increases to the age of twenty weeks, and then declines. The peak of susceptibility appears to be somewhere between the ages of twelve and twenty weeks. Finger[21] found that in a group of ninety-nine rats, fifty-five had exhibited seizures by the age of 90 days, seventy-four by the age of 120 days, and eighty-seven by 150 days. The experiments agree that after the age of 140 to 150 days, there is a decrease in susceptibility.

The results of experimentation on the inheritance of susceptibility to seizures have been controversial. In an early study, Maier and Glaser[22] reported the controlling

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[20] N. R. F. Maier and Nathan M. Glaser, "Studies of Abnormal Behavior in the Rat. X. The Influences of Age and Sex on the Susceptibility to Seizures during Auditory Stimulation," Journal of Comparative Psychology, 34: 23-28, 1942.

[21] Frank W. Finger, "Factors Influencing Audiogenic Seizures in the Rat: II. Heredity and Age," Journal of Comparative Psychology, 35: 227-232, 1943.

[22] N. R. F. Maier and Nathan M. Glaser, "Studies of Abnormal Behavior in the Rat. V. The Inheritance of the 'Neurotic Pattern.'" Journal of Comparative Psychology, 30: 413-418, 1940.

factor to be a simple Mendelian dominant, but the data of a later experiment "do not support a single Mendelian type of transmission".[23] Griffiths[24] found it possible, by selective breeding for six generations, to produce one group with a much higher percentage of convulsions than the original parents, and, by the same process, another group with a lower degree of susceptibility. The author concludes that his results suggest a genetic law in operation, but not a simple one.

Nutritional factors are becoming increasingly important in the study of all psychological phenomena. In experimentation with seizures, vitamins have received a great deal of attention, particularly those of the B-complex group.[25, 26] There is a decrease in the number of seizures exhibited when the diet is supplemented with vitamins B_1,

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[23] N. R. F. Maier, "Studies of Abnormal Behavior in the Rat. XIV. Strain Differences in the Inheritance of Susceptibility to Convulsions," Journal of Comparative Psychology, 35: 331, 1943.

[24] William J. Griffiths, Jr., "Transmission of Convulsions in the White Rat," Journal of Comparative Psychology, 34: 263-277, 1942.

[25] 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," Journal of Comparative Psychology, 33: 253-258, 1942.

[26] Robert A. Patton, op. cit., pp. 215-221.

B_2, or B_6, or brewer's yeast. A diet low in magnesium will produce an increase in the number of seizures, followed by a decrease when sufficient magnesium is replaced.[27] One study concludes that a diet adequate in quantity and quality would offer full protection against seizures;[28] there remains the problem of determining just what components make up a diet fully adequate.

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[27] R. A. Patton and H. E. Longenecker, "Studies on the Nutritional Basis of Abnormal Behavior in Albino Rats. V. The Effect of Pyridoxine Deficiency upon Sound-Induced Magnesium Tetany," Journal of Comparative Psychology, 38: 319-334, 1945.

[28] R. A. Patton, H. W. Karn, and C. G. King, op. cit., p. 258.

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[28] R. A. Patton, H. W. Karn, and C. G. King, op. cit., p. 258.

PROCEDURE

Equipment and testing procedure. The equipment for testing seizures was a box similar to that described by Maier and Glaser.[29] It consisted of a testing chamber, in which the rat was placed, separated by wire screening from another chamber containing lights and a motor attached to an arm on which were keys. The testing chamber was lined on four sides by rubber over felt to prevent injury to the rat, and the entire box was closed with a double glass door through which the rat was observed. Each rat in the experiment was tested in this box every other day for twenty days, a total of ten test trials.

The procedure for a single test was as follows: The rat was placed in the box and the motor was started. If the rat began wild, undirected running, a record was made of time in seconds from the beginning of the sound. If the rat evidenced a convulsion, *i.e.*, a rigid tremor, a record of time was made and the motor was turned off. If none of this behavior appeared, the sound was discontinued after two minutes and the rat was returned to the home cage.

A convulsion is always preceded by "blind" running

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[29] N. R. F. Maier and N. M. Glaser, "Studies of Abnormal Behavior in the Rat. V. The Inheritance of the 'Neurotic Pattern,'" *op. cit.*, p. 414.

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[29] N. R. F. Maier and N. M. Glaser, "Studies of Abnormal Behavior in the Rat. V. The Inheritance of the 'Neurotic Pattern,'" op. cit., p. 311.

of an unusually high velocity, seemingly without respect to obstacles such as walls; however, the running period is not always followed by a convulsion. Hence, each rat of this experiment received two test "scores": (1) a score if the running period occurred in a given test trial, termed a "running fit", and (2) an additional score if a convulsion followed. The results were overlapped, of course, since on any day a rat convulsed, he also received a score for a running fit. Although a seizure consists of all behavior present, the results are analyzed separately for each of these parts.

A convulsion may be followed by spasmodic jumping, or the rat may immediately lapse into a comatose phase. During the passive phase, the rats are very unresponsive to stimulation, exhibiting _flexibilitas cerea_, or waxy flexibility, a condition in which they offer little resistance to being molded into unusual postures. It has been shown that the passive phase is also characterized by low and irregular heart rates, acidosis, decreased blood carbon dioxide, and decreased clotting time of the blood.[30] Physical changes which were observed during or after the testing period were recorded with the seizure records.

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[30] Frank W. Finger, "Convulsive Behavior in the Rat," _op_. _cit_., p. 212.

Subjects. The parents for the experimental group were chosen from the regular laboratory colony by means of a series of four to six tests in the seizure box. Those chosen were of two classifications: two females and one male who showed no evidence of susceptibility to seizures during the testing period, and two females and one male who appeared to be the most susceptible available, *i.e.*, who displayed running fits, or running fits and convulsions, on the greatest number of occasions. The male originally chosen for the "susceptible" group did not impregnate the females within six weeks, so it was necessary to replace him with another male who displayed only running fits. All rats of the experimental group were offspring of these parents.

Each litter was weaned at the age of one month, and randomly separated into three groups. The first of these groups was given drinking water which contained 20 per cent lactose; the second group had 20 per cent dextrose in their water, and the third received plain water. All were reared on the standard laboratory food, Purina Chick Growena. The rats remained on the experimental diets until they had received tests for seizures. For one half of the litters, the testing began when they were ninety days old, and for the other half, when they became one hundred twenty days of age.

In addition to the seizure records, observations regarding any unusual aspects of health, growth, or behavior

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In addition to the seizure records, observations regarding any unusual aspects of health, growth, or behavior were recorded during the experiment. Differences observed among the three groups will be discussed in the section which follows.

Lactose and dextrose were utilized in this study only as additions to a standard diet. For simplicity in discussing the results, however, the groups will be referred to as follows: lactose-fed, indicating the group reared on a standard diet and given additional lactose in drinking water; dextrose-fed, referring to the group given dextrose in drinking water in addition to a standard diet; and water-fed, indicating the group given no additional sugar.

Factorial design. A factorial design was employed whereby the three experimental factors were varied simultaneously. As can be seen from Table I, each of twelve treatments was applied to a group of five rats, the variables in each treatment being designated by the letters A, B, and C. The capital letter _A_ indicates those offspring of normal, or non-susceptible, parents, while the small letter _a_ is for offspring from the susceptible parents. A capital _B_ designates the rats who were tested at the age of one hundred twenty days, and small _b_ those who were tested when ninety days old. The experimental diets are indicated by the letters _C_, for those on a diet including dextrose, _c_, for those on plain water, and _c'_, for those on lactose. For were recorded during the experiment. Differences observed among the three groups will be discussed in the section which follows.

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TABLE I

FACTORIAL DESIGN

	Rats					
Treatment	1	2	3	4	5	Sum
ABC						
ABc						
ABc'						
AbC						
Abc						
Abc'						
aBC						
aBc						
aBc'						
abC						
abc						
abc'						
Total						

A: normal parents
a: susceptible parents
B: 120 days old
b: 90 days old

C : dextrose
c : water
c': lactose

example, the letters ABC designate the five rats who were from normal parents, tested at the age of one hundred twenty days, and reared on a diet containing additional dextrose; abc' describes the animals from susceptible parents, tested at ninety days of age, and reared on the additional lactose diet.

RESULTS

The original data on the number of running fits and convulsions for each rat can be seen in Tables II and III. Analysis of variance of this data revealed no significant differences among the various experimental groups. The results of this analysis are shown in Tables IV and V. Following a suggestion made by Edwards,[31] it was determined that the means of the experimental groups tended to be proportional to the variances of those groups. This condition violates an underlying assumption necessary for the validity of the F-test: the variances must be homogeneous in order to insure independence of the mean squares. If the original data is transformed from whole numbers to the square-roots of those numbers, the means and variances no longer tend to be proportional, and the application of analysis of variance is more likely to be valid. The transformation of each score (X) to $\sqrt{X + .5}$ was used because the means of the various groups were small and the original data included many values of zero.[32] Analysis of variance was then applied to the transformed data, but this correction failed to change the resulting F-ratios to any extent. The A/V table for this

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[31] Allen L. Edwards, Experimental Design in Psychological Research, (New York: Rinehart and Company, Inc., 1950), p. 199.

[32] Ibid., pp. 199-200.

RESULTS

The original data on the number of running fits and convulsions for each group have been [illegible] in tables I, II, III. Analysis of variance of this data revealed no significant differences among the various experimental groups. The results of this analysis are shown in tables IV and V. Following a suggestion made by Edwards,[31] it was determined that the means of the experimental groups tended to be proportional to the variances of those groups. This condition violates an underlying assumption necessary for the validity of the F-test: the variances must be homogeneous in order to insure independence of the mean squares. If the original data is transformed from whole numbers to the square-roots of these numbers, the means and variances no longer tend to be proportional, and the application of analysis of variance is more likely to be valid. The transformation of each score (X) to $\sqrt{X + .5}$ was used because the means of the various groups were small and the original data included many values of zero.[32] Analysis of variance was then applied to the transformed data, but this correction failed to change the resulting F-ratios to any extent. The A/V table for this

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[31] Allen L. Edwards, *Experimental Design in Psychological Research*, (New York: Rinehart and Company, Inc., 1950), p. 129.

[32] *Ibid.*, pp. 199-200.

TABLE II

NUMBER OF RUNNING FITS IN TEN TRIALS

Treatment	Rats					Sum
	1	2	3	4	5	
ABC	0	0	0	10	0	10
ABc	9	9	0	0	0	18
ABc'	0	0	2	2	0	4
AbC	10	0	0	0	10	20
Abc	10	4	0	10	8	32
Abc'	0	0	10	0	10	20
aBC	0	0	8	1	10	19
aBc	10	0	0	0	0	10
aBc'	0	2	0	6	0	8
abC	2	9	0	0	10	21
abc	10	0	0	0	0	10
abc'	0	0	0	0	5	5
Total						177

A: normal parents
a: susceptible parents
B: 120 days old
b: 90 days old

C : dextrose
c : water
c': lactose

TABLE III

NUMBER OF CONVULSIONS IN TEN TRIALS

	Rats					
Treatment	1	2	3	4	5	Sum
ABC	0	0	0	7	0	7
ABc	5	5	0	0	0	10
ABc'	0	0	0	0	0	0
AbC	7	0	0	0	10	17
Abc	2	4	0	3	0	9
Abc'	0	0	0	0	4	4
aBC	0	0	0	1	6	7
aBc	10	0	0	0	0	10
aBc'	0	0	0	1	0	1
abC	0	1	0	0	9	10
abc	9	0	0	0	0	9
abc'	0	0	0	0	0	0
Total						84

A: normal parents
a: susceptible parents
B: 120 days old
b: 90 days old

C : dextrose
c : water
c': lactose

TABLE IV

A/V TABLE FOR RUNNING FITS

Source	df	Sum Sq.	Mean Sq.	F
Total	59	1042.85		
A	1	16.02	16.02	
B	1	25.35	25.35	1.36
C	2	36.30	18.15	
AB	1	18.01	18.01	
AC	2	40.03	20.015	1.07
BC	2	.10	.05	
ABC	2	13.05	6.525	
Exp. Err.	48	893.99	18.62	

TABLE V

A/V TABLE FOR CONVULSIONS

Source	df	Sum Sq.	Mean Sq.	F
Total	59	476.40		
A	1	1.67	1.67	
B	1	3.27	3.27	
C	2	39.90	19.95	2.27
AB	1	2.39	2.39	
AC	2	1.23	.615	
BC	2	5.83	2.915	
ABC	2	1.31	.655	
Exp. Err.	48	420.80	8.77	

For 48 and 1 df <u>F</u> is 7.19 at 1% level
4.04 at 5% level

For 48 and 2 df <u>F</u> is 5.08 at 1% level
3.19 at 5% level

transformation is presented in Table VI; inspection of the table will reveal that significance of the results was not altered.

It was also determined that the means of the original data for the experimental groups tended to be proportional to the standard deviations of those groups. The correction suggested for this condition is a transformation to a logarithmic scale, taking the form of log(1 + X) when zero values are included.[33] Following an example of Snedecor[34] this transformation was performed, using $\log_{10}(1 + X)$. Analysis of variance of the transformed data again failed to change the F-ratios to any appreciable extent. The resulting values can be seen in Table VII. Since the two applicable transformations failed to be of value for the data on running fits, they were not applied to the data on convulsions.

The statistic Chi-square is of value when hypotheses of frequencies are to be tested. Each observation must be independent, so that the number of rats displaying a certain type of behavior could be tested but not the number of seizures per rat, since the latter are not independent. Such tests were run but showed no statistical significance among

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[33] *Ibid*., p. 203.

[34] George W. Snedecor, *Statistical Methods*, (fourth edition; Ames: The Collegiate Press, Inc., 1946), pp. 448-451.

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[33] Ibid., p. 203.

[34] George W. Snedecor, Statistical Methods, (fourth edition; Ames: The Collegiate Press, Inc., 1946), p. 448-451.

TABLE VI

A/V TABLE
SQUARE-ROOT TRANSFORMATION FOR RUNNING FITS

Source	df	Sum Sq.	Mean Sq.	F
Total	59	101.179		
A	1	1.165	1.165	
B	1	1.734	1.734	
C	2	2.20	1.10	
AB	1	2.512	2.512	1.38
AC	2	5.796	2.898	1.59
BC	2	.257	.128	
ABC	2	87.191	.095	
Exp. Err.	48	87.329	1.819	

TABLE VII

A/V TABLE
LOGARITHMIC TRANSFORMATION FOR RUNNING FITS

Source	df	Sum Sq.	Mean Sq.	F
Total	59	11.329		
A	1	.141	.141	
B	1	.224	.224	1.11
C	2	.251	.1255	
AB	1	.30	.30	1.49
AC	2	.712	.356	1.77
BC	2	.023	.0115	
ABC	2	.024	.012	
Exp. Err.	48	9.654	.2010	

the three groups.

Table VIII was prepared to show trends toward inhibition of seizures by lactose. It can be seen from this table that there was little difference in the numbers of rats who exhibited seizure behavior; however, a difference apparently existed in the frequency of seizures per rat. Seven rats of the twenty reared on additional lactose were subject to a total of 37 running fits, or an average of 5.3 for each susceptible rat, while the other groups showed averages of 7.7 running fits per susceptible rat reared on additional dextrose, and 8.75 running fits per rat reared on water. Similarly, the average numbers of convulsions for the susceptible rats of each group were determined: For dextrose, 5.9, based on seven rats; for water, 5.7, based on seven rats; and for lactose, 2.5, based on two rats. The animals involved in this comparison were less than half of the entire experimental group, and no conclusions could be based on so small a sample. Although the differences have no statistical significance because of the very few rats concerned, they do seem to suggest a tendency for rats reared on lactose to have, on the average, fewer running fits and convulsions than their litter mates reared on water or dextrose.

Observations recorded during the experiment reveal further differences among the experimental groups. There was a tendency for rats reared on dextrose to exhibit running

TABLE VIII

FREQUENCY OF OCCURRENCE OF SEIZURE BEHAVIOR AND NUMBER OF RATS INVOLVED

Group	Number of Rats Showing Running Fits	Total Number of Running Fits	Average	Number of Rats Showing Convulsions	Total Number of Convulsions	Average
Dextrose	9	70	7.7	7	41	5.9
Water	8	70	8.75	7	38	5.7
Lactose	7	37	5.3	2	5	2.5

fits terminating with cyanosis and some waxy flexibility, without any actual convulsion, but, although this occurred more often in dextrose-fed rats, it was also observed on some occasions in the other groups.

The rats reared on dextrose and water were of equal size and seemed to be of equal health. Of a preliminary group of six rats, weaned at the age of 21 days and placed on the lactose diet, only two survived. These two were obviously stunted in their growth when compared to their litter mates on diets of dextrose or water. When subsequent litters, used for the experiment, were weaned at the age of thirty days, all survived, but some of the rats on lactose never became so large as those on other diets; the average weights of the three groups at weaning were approximately the same.

Most rats reared on lactose appeared to be highly nervous and emotional. They never became so tame as the animals on the other diets, and even after much handling, they scampered up the side of the cage when the door was opened or when any noise was made nearby. Urination and defecation were much more frequent in these rats than in the others when they were handled or placed in the seizure box.

During testing periods, lactose-fed rats appeared to be more frightened of the sound than the rats of the other groups, although they displayed seizure behavior less often.

In testing a group not used for the experiment, it was thought that seizure behavior might appear if the exposure to sound was of a greater duration; exposures up to three and one-half minutes failed to produce any different behavior. Some of the running fits which were exhibited by lactose-fed rats were not of the great velocity usually seen, nor did they appear to be so much without direction. The running was circular, but with fewer collisions with walls and ceiling of the testing chamber. Behavior of this type was not observed in rats on any other diet.

The differences noted in the lactose-fed group appeared to be more prevalent and exaggerated in the females than in the males. Because of their size and untamed behavior, ninety- to one hundred twenty-day old lactose-fed females appeared to be about sixty days of age. Except that they were thin, their appearance was otherwise normal for very young rats; no abnormalities of fur or coloring were noticeable.

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DISCUSSION

Statistical analysis of the data of this experiment offers no conclusion but that the quantity of lactose investigated has no effect upon the incidence of sound-induced seizures in rats. No statistical treatment employed offered any indication of significant differences among the experimental groups. Approximately the same number of rats in each group were proved susceptible to seizures by the testing procedure, and the frequency of seizure behavior was not significantly smaller or larger for any group.

That differences among the groups did exist was shown by observations of the animals recorded during the experiment. Running fits in lactose-fed rats were not followed by convulsions so often as they were in dextrose- or water-fed animals; also, lactose-fed rats did not exhibit running fits, on the average, so often as did rats of the other groups. Some of the running fits shown by lactose-fed rats were not qualitatively equal to those shown by other rats: they were neither so wild and undirected nor of so high velocity. The physical condition of lactose-fed rats was not equal to that of their litter mates reared on water or dextrose: they tended to be smaller, thinner, and more nervous and emotional than normal animals. Some of these factors must be attributed to the effects of lactose in the diet, since they were

not observed in rats on diets of water or dextrose.

Less than half of the entire group of animals used for this experiment showed any evidence of seizure behavior; only twenty-four of sixty rats exhibited one or more running fits, and only sixteen of the sixty were subject to one or more convulsions. The scores of zero for the other rats contributed nothing to the comparison of the frequency of seizure behavior, which reduced the size of the samples to numbers too small to be of statistical significance. It is possible that the differences observed were due to chance factors. However, a comparison of the frequency of seizures and subjective observations does suggest that there might be a tendency for lactose to produce some effect upon behavior that is different from that produced in rats that received comparable quantities of additional glucose, as a substitute for lactose, or that received no extra carbohydrate beyond that contained in the standard diet.

It is felt that further experimentation would be desirable before lactose is rejected as a possible influence upon behavior. A more simple experimental design, with larger numbers of animals, might produce different results from the present study. In the opinion of this experimenter, more striking effects might be produced if lactose were introduced into the diet before weaning. Lactose included in the diet of a nursing mother might possibly influence the

subsequent behavior of the litter. Since no appreciable differences were found in the first generations of offspring from normal and susceptible parents, and since no appreciable differences existed between the two ages included in this study, these factors might better have been held constant. This experiment consumed a period of one calendar year; since a relationship has been found between the season of the year at which the rats are born and the degree of susceptibility,[35] further investigation should perhaps be concentrated in a shorter period of time. What effect this factor may have had on the data of the present study cannot be determined. Perhaps an advantage could be obtained by limiting the experimental diets to two, lactose and no-lactose, thus enabling the size of the groups to be further increased. The primary concern of future experimentation should be to include greater numbers of animals.

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[35] E. J. Farris and Eleanor H. Yeakel, "The Susceptibility of Albino and Gray Norway Rats to Audiogenic Seizures," Journal of Comparative Psychology, 35: 73-80, 1943.

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SUMMARY AND CONCLUSIONS

An experiment was conducted to determine the effects of a diet including drinking water containing 20 per cent lactose on the incidence of sound-induced seizures in rats. These effects were compared to those of a diet including drinking water containing 20 per cent dextrose and a diet with no added sugar. The genetic background of the subjects of the experiment was varied, including offspring from normal, or non-susceptible, parents and offspring from parents susceptible to seizures. One-half of the subjects of the experimental group were tested for seizures at the age of ninety days, and the others were tested at the age of one hundred twenty days. No significant differences were found for any of the experimental factors. There appeared to be a tendency for rats reared on the diet including lactose to exhibit fewer evidences of seizure behavior than did their litter mates reared on diets including dextrose or with no added sugar. The differences observed among the experimental groups were not great enough to be of statistical significance. Further experimentation would be necessary to determine if a true difference could be produced.

The conclusions which may be drawn from this study are as follows:

(1) No significant differences in the incidence of

SUMMARY AND CONCLUSIONS

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The conclusions which may be drawn from this study are as follows:

(1) No significant differences in the incidence of

sound-induced seizures occur in the first generation of offspring from susceptible and non-susceptible parents.

(2) No significant differences in the frequency of seizure behavior occur between rats of the age of ninety days and rats of the age of one hundred twenty days.

(3) No significant differences in the number of rats susceptible to seizures, nor in the degree of susceptibility, can be produced by diets including drinking water containing 20 per cent lactose or 20 per cent dextrose.

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