neither decreases nor increases in its concentration in the brain consistently affect the rate of bar pressing at threshold, given that the animal is kept awake; results of studies which claim to show this effect (*1*, *3*) are best accounted for by variations in wakefulness and activity level, either as a result of direct drug action or as a secondary result of toxicity.

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Cataracts Produced in Rats by Yogurt

Abstract. *Rats kept on an exclusive diet of yogurt avidly ate the yogurt, grew at a normal rate, were normally active, mated, conceived, and gave birth to normal, healthy litters. However, all of the rats developed cataracts. Cataracts appeared in young rats 2 to 3 months, and in adult rats 4 to 6 months, after initiation of the yogurt diet. Cataracts first manifested themselves in small vacuoles at the periphery of the lens and then in small striae extending toward the center of the lens. These striae progressively became longer, more coarse, and numerous until they coalesced, finally forming a mature white lens. The high content of galactose in commercially available yogurt could account in full for appearance of cataracts in 100 percent of the experimental animals. The cataracts appear to be the same as those produced by diets with a high content of galactose.*

The observation that an exclusive diet of commercially prepared yogurt produces cataracts in rats was made (*1*) during experiments to elucidate factors responsible for the production in man of benign paroxysmal peritonitis (*2*).

The rats were housed in individual cages (*3*) with a revolving drum, a cyclometer, a nonspillable food cup, and a graduated inverted 100-ml water bottle. Fresh yogurt was offered each day in food cups used for our stock diet. Guards placed over these cups prevented spillage. Several kinds of commercially available yogurt were used, all prepared in essentially the same way.

Records of the number of revolutions of the drum, and of food and water intake and of vaginal smears, were taken daily. At weekly intervals, the rats were weighed and inspected for condition of hair, skin, and teeth.

In our initial experiments, four rats were given access to stock diet, yogurt, and water in separate containers to determine whether rats would freely eat yogurt when also given access to a stock diet. All four rats ingested large amounts of yogurt and greatly reduced their intake of the stock diet. They drank very little water. They all grew at a normal rate, were normally active, and remained in apparently excellent health.

Then, four rats were kept on an exclusive diet of yogurt and water. They ate large amounts of yogurt, grew normally, and drank only small amounts of water. Estrous cycles in all four were regular. When mated, three rats conceived and gave birth to normal, healthy litters which were nursed and cared for until time of weaning. Two of these rats later gave birth to normal litters. These observations thus indicated that yogurt alone appeared to be a complete diet.

However, after these four rats had been observed for several months, it was noted by chance that all had developed bilateral mature cataracts. The changes in the lenses had escaped notice until then, because we had not been especially looking for them. Only when the cataracts were mature were they discovered. To our knowledge, no rat of the 40-year old colony had ever developed a cataract spontaneously.

We next designed studies to determine (i) rapidity of development of lens changes after initiation of the yogurt diet; (ii) frequency of occurrence of lens changes; (iii) age predilection, if any, in the rat for the development of these changes; (iv) the clinical evolution of these changes; and (v) clinical features of these cataracts compared with those produced by other experimental methods. We also hoped to determine what factor in the diet of yogurt produced the lens changes.

Twenty-six rats, 34 to 221 days old at onset of the diet, were used. Our observations made on six of these young animals (three males and three females) will be described in some detail as they are typical of the results obtained with

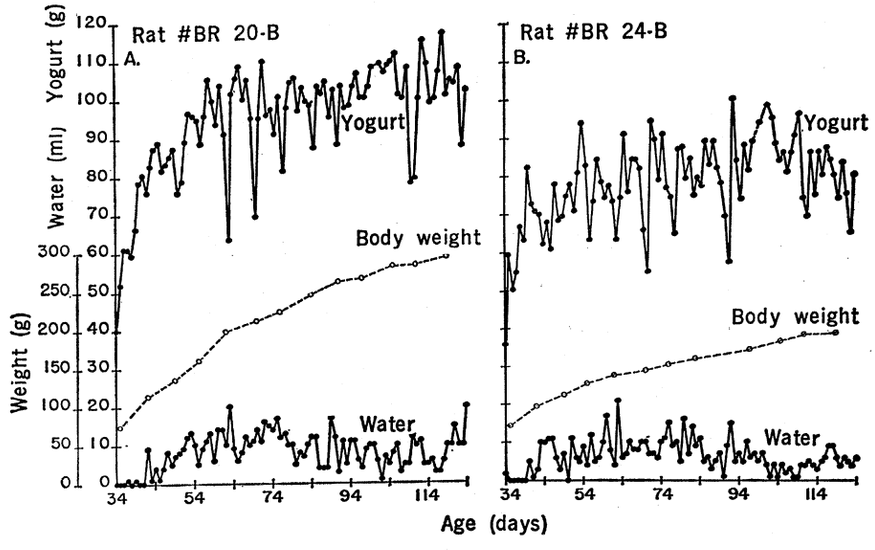

Fig. 1. Typical records of daily intake of yogurt and water over 90 days for a male (A) and a female (B).

other rats. Also, they will be compared with observations on a control group of 24 rats of the same age kept on stock diet.

The rats ate large amounts of yogurt almost from the first day. One typical male ate, on the average, 108 g per day; a female, 80 g (Fig. 1). Both drank very small amounts of water. Over 90 days the male gained in weight from 50 to 305 g; the female, from 68 to 200 g. Both appeared to be in excellent condition, free from any signs of deficiency. The rats on the yogurt diet ingested much larger amounts of water (from the yogurt and the drinking water) than did the control rats; they grew at a nearly normal rate.

In spite of the large differences in actual intake in grams of the stock diet and the yogurt diet (Fig. 2), intake values in calories per kilogram of weight were almost the same for control and experimental rats of all ages. This is a further demonstration that rats choose their diets on the basis of caloric intake (*4*).

None of the rats, even those that were followed for over a year, showed any obvious abnormality except for cataracts. There was no evidence of loss of hair, dermatitis, defects of teeth, diarrhea, incoordinate gait, or convulsive movements (*5*).

At termination of the study (which varied from 30 to 500 days), the animals were decapitated and autopsied. The only abnormalities noted were that three of the rats had enlarged ceca and one had hydrocephalus. Liver, pancreas, thyroid, gonads, and pituitary were stained with hematoxylin and eosin. No histologic abnormalities were noted. Blood collected after decapitation had normal numbers of red and white cells, eosinophils, and normal differentials. Concentrations of sodium and potassium in the blood were normal; those of calcium and phosphorus were slightly elevated. The hematocrit was low in a few rats. This was the only hematologic abnormality.

Using the Haag-Streit slit lamp, we examined the dilated pupils at weekly intervals. Changes in the lenses were first manifest as tiny vacuoles or fine white striae in the cortex at the periphery or equator (Fig. 3, A and B). These striae next extended from the equator toward the center both anteriorly and posteriorly (Fig. 3C). Patchy clouding of the anterior capsule occurred in some lenses, and posterior subcapsular opacification was a

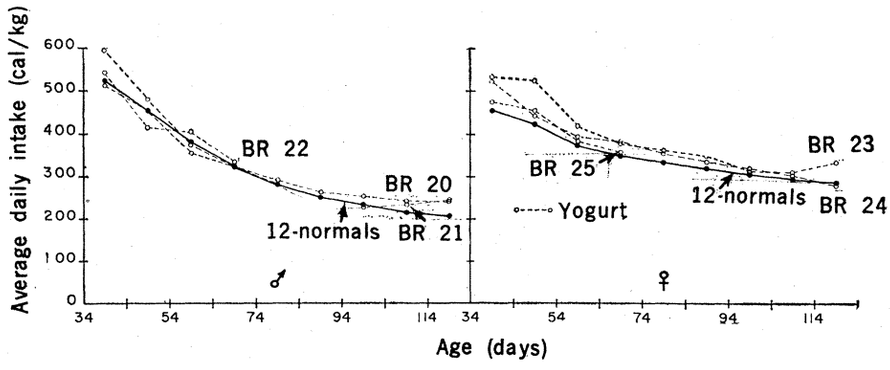

Fig. 2. Average (10 days) food intake for 12 females and 12 males on a stock diet (solid black lines) and for three males and three females on the exclusive yogurt diet (broken lines).

usual finding. The cortical striae then became more numerous and often more coarse, while vacuoles tended to disappear. The coarse cortical striae then coalesced or fragmented into granules, leading to a gradual complete opacification of the cortex—often with the separation of the Y suture (Fig. 3D). Nuclear haze and opacification were a late development. The end result was a mature white lens (Fig. 3E).

Onset of lens changes appeared to be related to the age of the rat at the time the diet was initiated. The six youngest rats on the diet were 34 days old. They developed initial cortical striae between 28 and 42 days after start of the diet. In the six rats started on the diet at 221 days of age, cortical striae were first noted between 68 and 83 days later. Thus, lens changes appeared more quickly in the younger animals.

The relationship of rapidity of maturation of lens changes to age of the rat at onset of the diet was less clear-cut. For example, one rat, started on the diet at 43 days of age, developed cortical striae after 1 month on yogurt. Seven months later, the changes had not progressed significantly. Another rat, started on the diet at age 75 days, had mature lenses after only 2 months on the diet. In general, however, the adult rats tended to have mature cataracts after 4 to 6 months on the yogurt diet.

Cataracts can be produced by diets deficient in various substances, for instance, riboflavin (*6*) or tryptophane

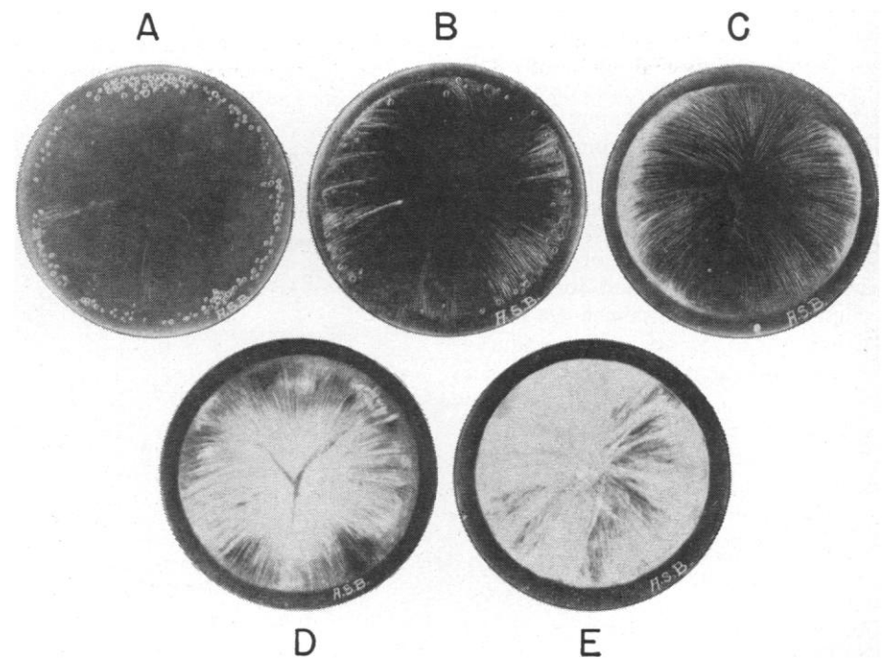

Fig. 3. Slit-lamp drawings of lenses illustrating various stages in development of cataracts resulting from a yogurt diet.

(7). In such states, lens changes are accompanied by a wide variety of other manifestations such as loss of weight, inactivity, and inability to reproduce. Rats on yogurt, however, showed no such signs or symptoms of dietary deficiency. Thus, their cataracts must have some other origin.

Yogurt is made from whole milk. The carbohydrate of milk is lactose which breaks down into equal parts of glucose and galactose. Attention is immediately centered on galactose, in view of the findings that a diet with a galactose caloric percentage of 22 percent was sufficient to produce cataracts in rats (8). However, in caloric content, galactose comprises only 14.4 percent of whole milk and only 14.2 percent of yogurt made from whole milk (9). Both of these values are well below the cataractogenic level.

Analysis of the commercially produced yogurt used in our study revealed a much higher content of galactose—from 22 to 24 percent, a value definitely within the cataractogenic range. This striking difference between the galactose content of the commercial yogurt we were using and that of the standard analysis of yogurt prompted us to discuss this discrepancy with the manufacturers of the yogurt.

We learned that yogurt made in this country is no longer simply the product of fermentative action of the *Lactobacillus bulgaricus* and *Streptococcus thermophilus* upon whole milk. Most of the butterfat in the milk is removed before its conversion to yogurt. Removal of butterfat produces a milk which has, relatively speaking, more carbohydrate—and thus more galactose. However, yogurt made from such milk is thin and watery. To improve the consistency, manufacturers add skim milk powder, thus further increasing the caloric percentage of galactose. These procedures account for the elevation of the caloric percentage of galactose in the commercially produced yogurt to cataractogenic level for rats.

As evidence that cataracts produced by the yogurt diet result from its high content of galactose is the fact that cataracts produced by yogurt and galactose are clinically indistinguishable.

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Phycomyces: Habituation of the Light Growth Response

Abstract. Phycomyces *sporangiophores respond to four distinct physical stimuli: gravity, light, stretch, and an avoidance stimulus. Saturating the organism with a light stimulus so that it does not respond to any additional light program does not decrease its ability to respond to an avoidance stimulus. This demonstrates that the organism has the potential to respond after a saturating light stimulus and that the avoidance stimulus acts at some point past or parallel to the light-receiving mechanism.*

The stage IV sporangiophore of the fungus *Phycomyces* has been the object of intense study in numerous laboratories over the past decade. It responds quantitatively to several distinct stimuli: light, stretch, and gravity, and in addition has the ability to grow away from solid objects (1). This last property has been termed avoidance, and it has been the least studied and the most poorly understood of the properties.

We now present further experiments on the mechanism of the light growth response. Several papers describe in detail the response of *Phycomyces* to light (1, 2). The light growth response occurs when the intensity of stimulating light is greater than that to which the organism has become adapted. After several minutes at the higher intensity, an increase in growth occurs which sometimes leads to a doubling of the initial growth rate. But, after approximately 5 minutes, the rate begins to decrease again to the initial basal growth rate of about 3 mm/hour. Now the organism must adapt to the new light intensity before it will respond to a further increase in light. After the initial increase in light intensity, there is a period during which additional light stimuli will not cause a full increase in growth. This return to a state of sensitivity has been described in an equation that is similar to one describing the charging of a capacitor (3). In 1966 Castle (4) proposed a model in which an increase in growth depleted a pool of substrate to a point below which further increase in growth could not be evoked. This model makes possible a very simple prediction. If the organism were unable to respond to a second light stimulus because of depletion of substrate, it should also be unable to respond to any of the other stimuli.

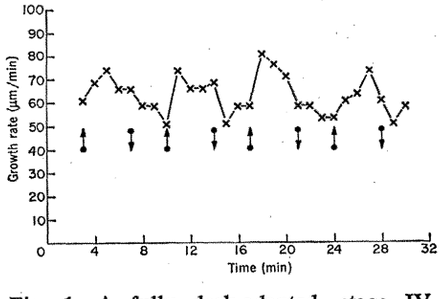

Fig. 1. A fully dark-adapted, stage IV sporangiophore stimulated by a double barrier at the times indicated with an upward arrow ↑. Removal of the double barrier is indicated by a downward arrow ↓.