

In all the infections in these experiments, a highly virulent strain of human tubercle bacilli (#4008) was used, and a standard amount (1 mg.) of fine suspension was injected intravenously into the ear vein. All treatments with streptomycin were given by subcutaneous injection.

In a series of preliminary experiments in which the persistence of streptomycin effect was studied, using a sufficiently large number of controls (6) and an equal number of streptomycin-treated animals (given 25,000 units of streptomycin daily for 82-91 days and infecting intravenously one day after the last treatment), the average duration of life of the controls was 22 days compared with 29 days for the pretreated animals. When the pretreatment with a similar amount of streptomycin daily continued for only two weeks, the average duration of life of the controls was 21 days; and for animals pretreated with streptomycin, it was 22 days, which is about the same, although the spleen size was perceptibly less in the treated animals. In single injections, 50,000 units of streptomycin were not lethal, while 100,000 units were frequently fatal in our tests on normal animals.

In order to compare the results of the injection of 4 doses of streptomycin daily for a total of 25,000 units with a single injection of 25,000 units daily and 25,000 units given at 5-day intervals in a single injection, several sets of duplicate experiments were performed. Four to 6 or more guinea pigs were used in each test as well as infection control animals given only the intravenous injection of 1 mg. of virulent human tubercle bacilli in fine suspension without treatment with streptomycin. While the average duration of life of the control infected guinea pigs varied within the narrow limits of 19-21 days, that of the animals given 4 daily injections to a total of 25,000 units daily was from about 100 to about 150 days. Those given the 25,000 units at 5-day intervals, starting 6 days prior to infection and continuing throughout infection, were also alive beyond 100 days in most instances.

In these experiments it was noted that individual animals would die of a generalized tuberculosis in spite of intensive treatment with streptomycin and regardless of whether the injections were given daily or at 5-day intervals.

The appended 14-week weight graph (Fig. 1) illustrates the effects of 4 daily injections (for a total of 25,000 units) of streptomycin, one single daily injection throughout the experiment, and single injections of streptomycin at 5-day intervals compared with infection controls. In the series in which the streptomycin was given only as a single injection of 25,000 units at 10-day intervals, the treated animals outlived the controls, so that the average of the controls was 20 days and that of the treated 70 days.

The foregoing experiments would appear to indicate that streptomycin does not act in tuberculosis as a simple chemotherapeutic retardant as it does in the test tube (since simple *in vitro* acting and *in vivo* distributed chemicals fail to affect tuberculosis), but that there is a threshold of remote sustained action. When initiated minimally, the effect persists for some time; above the maximum threshold effect, it is needless to continue forcing treatment, since the benefit derived does not exceed that of the established maximum. This information should extend the present use of streptomycin as an adjunct to the treatment of human tuberculosis and make streptomycin available for human treatment where excessive administration previously was economically prohibitive to certain cases.

It would appear that the amount and frequency of administration of streptomycin in tuberculosis can be reduced without appreciable loss of effectiveness. It is felt that the intimate mechanism of streptomycin action in tuberculosis still remains to be disclosed satisfactorily.

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A Possible Role of Food Purification in the Etiology of Dental Caries

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A study (3) has been made of factors influencing the caries susceptibility of rodents (36 mice, 53 Syrian hamsters, and 153 Long Evans strain rats). It has been possible to produce dental caries similar to that in man by feeding a finely powdered, purified ration (1) containing 67 per cent purified carbohydrates, primarily sucrose, and complete in known nutritional essentials. Caries did not develop in the mice and rats and was limited in the hamsters unless the experimental feeding on the purified diet was commenced during tooth development.

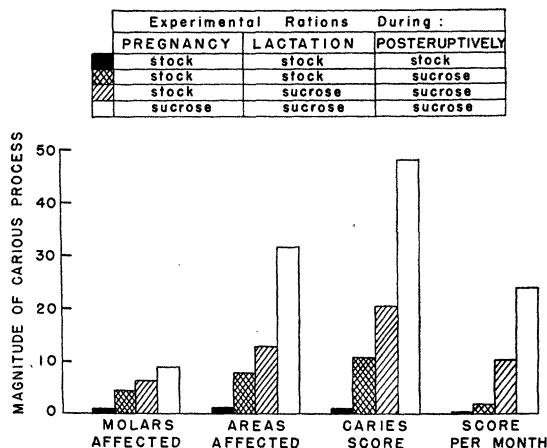


FIG. 1. The caries incidence of groups of hamsters whose experimental feeding on the purified ration was commenced before, during, and after tooth developments, respectively; their molars decayed in a ratio of 20:10:2. ("Sucrose" diet refers to the purified ration, containing 67 per cent sucrose. "Stock" diet refers to the Purina laboratory chow.)

The caries susceptibility appears to be greatly influenced by a mechanism (possibly an unrecognized nutritional factor) operating before tooth eruption from conception to maturation of the offspring and their individual teeth (see Fig. 1). In the light of these results a reinterpretation has been made of earlier observations in animals and man.

A review of previous failures to produce caries in various animals (3), including the primate, fed purified high sucrose diets suggests that the experimental feeding started out with

too old animals, did not extend to second generations, or covered too short periods within one to overcome caries-resisting properties of the species, strain, or teeth in question.

An over-all analysis has been made of the trend of dental caries in about 800,000 children (2) surveyed by various workers in 11 European countries during the last 50 years. Following drastic reductions in consumption of refined carbohydrates at the beginning of the two World Wars, a marked caries reduction can be demonstrated. But the time relationship between the decrease in sugar consumption and the reduction in caries cannot be explained on the basis of a rapid mechanism in the oral environment. There is a delay of several years in the initial effect and a lag of many years in the terminal "effect

may be in the nature of an unrecognized indirect influence upon the quality of the offspring and its developing teeth, and that the effect may be accumulated through generations.

The hypothesis of an accumulative depletion of a nutritional factor or combination of factors favorable to the developing teeth is being tested.

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Effect of Tetraethylammonium Chloride in Experimental Gastric Ulceration in the Rat

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Recently a method has been described for the uniform production of gastric ulceration in the rat (4). This method, or a modification of it, has been used to test the effectiveness of antiulcer factors (5). Harkins has reported (2) the complete prevention of gastric ulceration in rats by transabdominal vagotomy, using this method.

It has been shown (1) that the tetraethylammonium ion blocks the transmission of impulses at autonomic ganglia. In view of the reported effectiveness of vagotomy in preventing gastric ulceration in the rat and the widespread use of vagotomy in the clinical treatment of peptic ulcers, it was thought that the tetraethylammonium ion might prove useful in the therapy of this condition. Therefore, the effectiveness of this compound in preventing gastric ulceration in the rat has been studied.

Eighteen female rats weighing 80-100 grams were fasted for 72 hours. The rats were kept separated in cages with a wide wire-mesh bottom and were given water throughout the fasting and experimental period. They were anesthetized with ether. A short midline incision extending downward from the xiphoid process was made and the pylorus carefully exposed and ligated. The incision was closed with sutures, and the wound was covered with a thin coating of flexible collodion.

Alternate rats were injected intramuscularly with 1 mg. of tetraethylammonium chloride (Etamon chloride,² 1 ml. of saline solution) just prior to the pyloric ligation and at hourly intervals thereafter until death or until the animal was sacrificed.

The results are summarized in Table 1. Rat #1 died as a result of anesthetization, and rat #9, a control, has been omitted from the series because it was found dead 2.5 hours after pyloric ligation and showed no lesions at autopsy. It

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THE DISCREPANCY (TIME-LAG)

between

WAR-TIME - REDUCTION

[FROM PREWAR LEVEL]

of

1.  SUGAR CONSUMPTION — (i.e. change in oral environment) &
2.  CARIOUS PERMANENT TEETH OF 7-YEAR OLDS (i.e. effect on the newly erupted teeth)

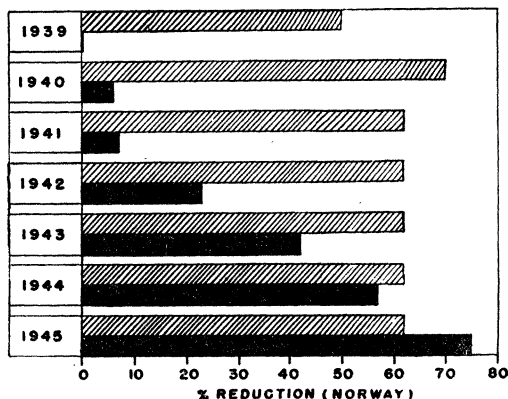


FIG. 2. A comparison of groups of 7-year-old children during each year of the war. Their permanent teeth after eruption were exposed to a similar sugar concentration in the oral environment. Significant caries reduction is seen in the teeth of those groups (1943/45) whose teeth had the longest "exposure" to the wartime diet before eruption, i.e. during development and final maturation.

of the wars" upon the caries reduction. This time factor can best be explained by an accumulative favorable effect before the teeth erupted into the oral environment (Fig. 2).

The mechanism of this beneficial influence upon the teeth developing during the war is not known. It cannot be attributed to any obvious, over-all uniform increase in the consumption of any previously demonstrated caries-inhibiting food or food factor, but may be related to the fact that the bulk of the caloric intake during the wars was in the form of natural foods. The large caloric loss resulting from the sugar and fat rationing primarily seems to have been compensated for by an increased consumption of nonpurified carbohydrates, potatoes, cabbage, and wartime bread (containing 80-95 per cent of the grain).

In view of these experimental and clinical observations, it is possible that the long-suspected relationship between dental caries and the excessive consumption of refined carbohydrates