Increased Incidence of Nontasters of Phenylthiocarbamide among Congenital Athyreotic Cretins

Abstract. The incidence of nontasters for phenylthiocarbamide was found to be significantly higher in 27 athyreotic cretins than in normal adults and children. A significant increase of nontasters among the parents and siblings of these cretins was also found. These findings are discussed in relation to maldevelopment of the fetal thyroid in nontaster genotypes.

The ability to taste phenylthiocarbamide is an example of a human genetic polymorphism (*1*) with most of the observed variations in taste thresholds being accounted for by simple monogenetic recessive inheritance (*2*). Nontasters are homozygous for the recessive allele (tt) and tasters are homozygous (TT) or heterozygous (Tt) for the dominant allele.

In 1942 Richter and Clisby (*3*) showed that phenylthiocarbamide was associated with hypertrophy of the rat thyroid, and a higher than normal incidence of nontasters was later observed in patients with nontoxic goiters (*4*). This relationship of thyroid disease to taste response prompted the following investigation of congenital cretins and their families.

The patients studied were all thoroughly documented examples of sporadic athyreotic cretinism, which is the most common cause of hypothyroidism in childhood. In 24 of the 31 cases studied, either a serum protein bound iodine or an I^{131} accumulation, or both, supported the diagnosis. Such children have congenital absence of the thyroid gland, and within 4 to 12 weeks after birth they exhibit marked decrease in growth rate and physiological evidence of hypothyroidism. Although rare examples of recurrence of the condition within the same sibship have been reported, there is no evidence that the condition is inherited.

The parents and adult controls were tested with 14 concentrations of phenylthiocarbamide according to the method of Harris and Kalmus (*5*). Their threshold was the weakest concentration at which they were able to differentiate four beakers of water from four beakers of the test concentration. The testing of children and infants was carried out by serially increasing the concentration until the bitterness was detected. This was repeated in most cases until the threshold was established by three responses at the same concentration. Within the childhood controls there was no significant difference in threshold with age, and the distribution was similar to that of the adults. Over 95 percent of the patients and controls were of European ancestry.

The results are shown in Fig. 1 and are expressed by threshold concentration tasted. Dilution 1 is 1300 mg/liter, and each subsequent number is one-half the strength of the preceding concentration. The histogram for the controls is shown in Fig. 1*A* and exhibits bimodality. For purposes of this study, the dividing line between taster and nontaster was placed between concentrations 4 and 5.

By utilizing clinical material from other pediatric endocrine clinics (*6*), 30 families containing 31 cretins were tested by the same observer, and all but four cretins could be tested accurately. It was found that 18 were nontasters and nine were tasters, as compared to the control group of 29 nontasters and 104 tasters. This is a significant difference ($\chi^2 = 22$, D.F. $= 1$, $P = < .001$). Thirty of the mothers were tested and 15 were nontasters, and of the 27 fathers tested, 12 were nontasters. Of the 29 unaffected siblings who were available for study, 18 were nontasters. The incidence of nontasters among parents and siblings of cretins as compared to normal is significantly increased ($\chi^2 = 21.6$, D.F. $= 1$, $P = < .001$).

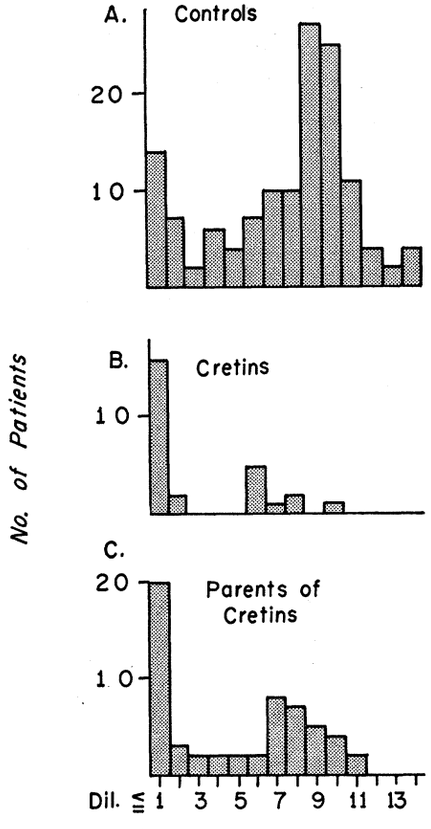

Fig. 1. Threshold dilutions of phenylthiocarbamide for the members of three groups. Dilutions 1 to 4 designate a nontaster; dilutions 5 to 14, a taster.

The demonstration of an association between nontasters for phenylthiocarbamide and athyreotic cretins raises the question as to the nature of the gene-environmental interaction involved in the development of this form of cretinism. It is well known that goitrogenic thiocarbamide substances are found in food (*7*), and it is possible that nontaster fetuses may be susceptible to embryonic thyroidectomy by these chemicals. The time, dosage, and duration of exposure of the fetus to maternally ingested goitrogens would most likely be critical, and variations in these factors could explain the fact that most of the nontasting siblings of cretins are normal.

If the preceding hypothesis is correct, one would expect a lower incidence of athyreotic cretinism among populations (for example, Chinese and Negro) where the incidence of nontasting is low or in countries where the diet contains minimal amounts of thiocarbamides (*8*).

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Rewarding Properties of Intracranial Stimulation

Abstract. Monkeys can be trained to press a lever to obtain intracranial brain stimulation on a large fixed-ratio schedule as well as on a continuous reinforcement schedule. A long extinction curve appears to be indicative of a future high fixed-ratio performance.

Previous reports by Olds and Milner (*1*) and Seward, Uyeda, and Olds (*2*) have indicated that behavior rewarded by intracranial stimulation has a low resistance to extinction. Schedules of