bridge (*9*, Fig. 1), the submergence sequences may be considerably more complicated than our Fig. 1 indicates. Because three of our trees were killed by rising salt water during two of Fairbridge's postulated regressions of sea level [see also Hussey (*4*, Table 1), 3250 ± 200 B.P.], their deaths would have to be explained by crustal downwarping at rates in excess of the eustatic regressions.

We wish to withhold judgment on these speculations, pending C^{14} dating of six samples from stumps at intermediate altitudes at each of the three sites (*10*).

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Antithyroid Effects of Aminotriazole

Abstract. Aminotriazole, like other antithyroid compounds and low-iodine diets, produces adenomatous changes in the thyroid glands of rats when fed continuously for long periods. Such changes are reversible if the antithyroid regime is discontinued. The antithyroid compounds that are naturally present in food are not regarded as causes of cancer.

The action of the Food and Drug Administration in seizing shipments of cranberries containing alleged residues of the herbicide aminotriazole (3-amino-1,2,4-triazole) (*1*) makes it desirable to summarize briefly some unpublished findings with this substance (*2, 3*).

A large number of compounds have the property of inhibiting the thyroid gland from reacting with inorganic iodide to form the thyroid hormone (*4*). Prominent among these "antithyroid" compounds are certain substances containing the –NH–CS– grouping, including thiouracil, and a number of aminoheterocyclic compounds, including aminotriazole (*5*). Many foods, including cabbage, turnips, peas, beans, strawberries, and milk, contain antithyroid substances (*6*), one of which, L-5-vinyl-2-thiooxazolidone ("goitrin"), has been isolated in quantities as high as 200 parts per million from rutabagas and has a potency equal to that of thiouracil as measured in human subjects (*7*).

In experiments in our laboratories (*3*) enlargement of the thyroid gland in rats and pronounced lowering of uptake of administered radioiodine by this gland were produced by feeding diets containing 60 or 120 parts per million of aminotriazole for 2 weeks. There were no significant changes in the gland at levels of 15 and 30 parts per million.

In studies carried out at a consulting laboratory (*8*), rats were fed diets containing 0 (group 1), 10 (group 2), 50 (group 3), and 100 parts per million (group 4) of aminotriazole. After 24 months the animals were sacrificed and a histological examination was made of some of the thyroid glands. No tumors were found in five thyroid glands examined in group 1, although there was one cystic follicle with papillary change that is typically the forerunner of a very large cystic adenoma. One adenoma was found in ten thyroid glands in group 2. Two of the 15 glands in group 3 and 17 of the 26 glands in group 4 were found to be adenomatous. One gland in group 3 and four in group 4 showed changes which were interpreted by some pathologists to be adenocarcinomatous and by others to be nonmalignant. The exact significance of these changes in relation to spontaneous thyroid pathology in rats of this age needs extended discussion beyond the scope of this brief article and will be reported elsewhere (*2*). After 17 weeks, aminotriazole was withdrawn from the diet of a fifth group of rats that had received 500 parts per million, and 2 weeks later their thyroid glands were found to be normal in appearance.

It has long been recognized that suppression of the function of the thyroid gland in rats by administration of antithyroid compounds or by deprivation of dietary iodine leads to an increase in the production of the thyroid-stimulating hormone of the pituitary and a consequent increase in the size of the thyroid gland (*9*). The prolongation of either type of regimen led to the emergence of thyroid adenomata (*9, 10, 11*) which were not seen when the feeding of the antithyroid diet was alternated with periods of control diet (*10*).

By continuing the feeding of comparatively high levels of such antithyroid substances as thiourea and thiouracil to mice, lung nodules of thyroid-like tissue were eventually produced (*12*). Adenocarcinomatous tumors were produced in rats by prolonged treatment with thiourea. No metastases were found and the authors regarded this absence as evidence against any direct carcinogenic effect of thiourea, but rather as reflecting the overproduction of a normal body constituent, thyroid-stimulating hormone (*13*).

These and other observations make it apparent that an antithyroid regimen in experimental rats and mice can be predicted to result eventually in the appearance of thyroid tumors. Some of these may reach a stage that is regarded by some authorities as adenocarcinomatous, although this point is debated by other investigators who consider the changes as resembling benign tumors (*14*). In any case, such a stage has been described only if the treatment corresponded to complete blocking of the thyroid gland taking place continuously for most of the normal lifetime of the animal. Moderate or intermittent treatments with antithyroid substances have not been reported to lead to the production of tumors. Indeed, the consumption of foods that inherently contain antithyroid substances is not usually regarded as a potential cause of cancer in human beings. Furthermore, thiouracil and its congeners are commonly used clinically in the treatment of hyperthyroidism, thus giving additional clinical experience in the use of compounds of this type (*15*).

Recently Hoshino has reported in a preliminary communication that injections of aminotriazole significantly delayed the production of liver cancer in rats that received the carcinogenic dye, 4-dimethylaminoazobenzene (*16*). This recalls the finding by Paschkis and coworkers (*17*) that another antithyroid compound, thiouracil, protected the livers of rats against the carcinogenic action of 2-acetaminofluorene.

The characterization of the antithyroid compound aminotriazole as a cancer-producing substance would seem to be questionable and in any case needs careful definition of conditions. Foods containing antithyroid substances are universally present in ordinary diets.

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Discrimination of Tones during Reinforcing Brain Stimulation

Abstract. Hungry animals were trained to press a lever for brain stimulation. Different tones were presented concurrently with the stimulation. A second lever delivered food only during critical tone periods. Animals were able to discriminate tones presented concurrently with rewarding intracranial stimulation, and they also interrupted self-stimulation behavior to respond appropriately under other reinforcements.

Since the report by Olds and Milner (*1*) that rats will perform tasks if rewarded by electrical stimulation of specific subcortical brain areas, a number of studies have demonstrated the phenomenon with guinea pigs (*2*), cats (*3, 4*), and monkeys (*5, 6*). The phenomenon may be referred to as self-stimulation when the animal is permitted to determine the rate of intracranial stimulation by its rate of responding. Previous studies have reported the distribution of rewarding sites within the central nervous system (*7*), the effect of various schedules of intermittent reinforcement on self-stimulation behavior (*8, 9*), the rate of extinction following the withholding of intracranial stimulation (*8, 10*), and the effect of various states of deprivation such as food and sex deprivation (3, *11*).

Little information is available, however, concerning the ability of an animal to respond to stimuli during intracranial stimulation. There is evidence that animals are unresponsive to environmental cues while receiving rewarding brain stimulation. In conditioned emotional response experiments, for example, animals stop working for food if a clicking sound which had previously been associated with a painful shock is presented (*12*), but Brady (*5*) has recently demonstrated that when rewarding brain stimulation is substituted for food, animals continue responding during the period of clicker presentation. Are the animals capable of sensing and interpreting stimuli presented concurrently with intracranial stimulation? The experiment reported here was designed to answer this question. The results also shed some light on the ability of animals to interrupt self-stimulation to respond under other kinds of reinforcement.

Seven male albino rats, weighing approximately 300 gm each at the beginning of the experiment, served as the subjects. Bipolar electrodes were implanted stereotaxically in the middle and posterior hypothalamus. Postoperatively, the rats were deprived of food until their weight was reduced to 80 percent of their weight on an ad libitum feeding regimen, and then were maintained at this weight. They were then trained to press a lever to receive a 0.2 ml cup of diluted condensed milk.

Tone discrimination training consisted of presenting 1.5-minute periods of tone A (1000 cy/sec) and tone B (200 cy/sec) in a random sequence. Responses were rewarded with milk only during tone A periods. When more than 80 percent of the responses occurred during the tone A periods, the subjects were trained to press a second lever for brain stimulation. The electrical stimulus consisted of a 0.5-second train of paired biphasic square waves presented at a frequency of 100 presentations per second. The pulse pairs were 0.2 msec in duration, and they were separated by an interval of the same duration. Responsiveness to the intracranial stimulation varied, and an intensity was selected which yielded stable lever-pressing rates.

After stable response rates for brain stimulation were established, 1.5-minute periods of either tone A or tone B were randomly presented with an average interval of 3 minutes between periods. During each tone period, every response on the brain-stimulation lever produced the appropriate tone. The onset of the tone followed the onset of the brain stimulus by 15 msec and ended 30 msec before the termination of the stimulus. If the animal switched to the food lever during a tone period, the tone started beeping independently of lever presses for the balance of the 1.5 minutes. The ending of the beeping tone served as a signal to the animal that food was no longer available. Thus, until the animal had switched to the food lever, tones were presented only concurrently with brain stimulation. Pressing the food lever was rewarded only during the tone A periods, while brain stimulation followed all responses on the brain-stimulation lever. Each test contained nine tone A and nine tone B periods.

There is clear evidence that the rats were able to discriminate between tones presented concurrently with brain stimulation. Figure 1 shows the activity of a typical rat on the brain-stimulation and food levers after eight testing sessions. Pressing of the food lever is indicated on the horizontal, while activity on the brain-stimulation lever is cumulated in the upper curve. The pen recording brain-stimulation-lever activity was deflected downward during the tone periods; these can be identified from the labels. It can be seen that the animals switched to the food lever only during tone A periods and returned

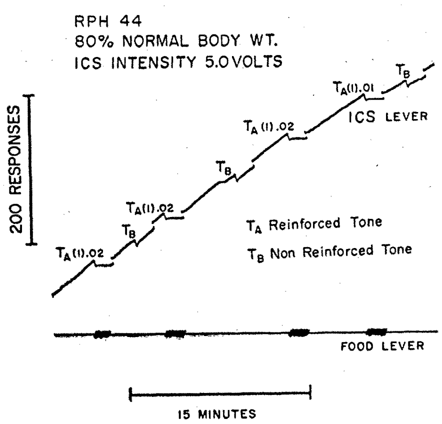

Fig. 1. Typical record illustrating responses on the intracranial stimulation (ICS) and food levers.

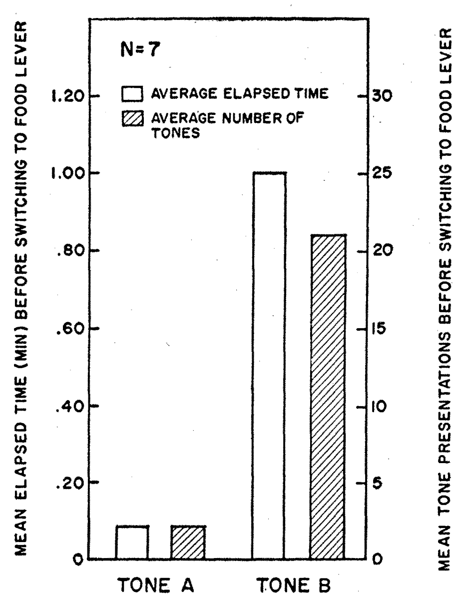

Fig. 2. Bar graph illustrating mean elapsed time and mean number of tone presentations before the switch to the food lever.