rate-limiting synthetic enzyme, should prove useful in this respect. The discovery of inhibitors, such as *p*-chlorophenylalanine, may also lead to therapeutic agents which would be effective in control of the exaggerated hydroxyindole pathway of tryptophan metabolism in patients with the carcinoid syndrome.

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Association of Illness with Prior Ingestion of Novel Foods

Abstract. *Rats were permitted to ingest a novel food and a familiar food. One hour later they were x-irradiated. When they were subsequently allowed to choose between these foods, their preference for the novel food was less than that exhibited by appropriate controls.*

If animals eat a particular food a few hours before they are x-irradiated, they will subsequently avoid that particular food because they associate the early symptoms of radiation sickness with it (*1*). Furthermore, injection of apomorphine, which like x-irradiation produces a gastrointestinal syndrome, also results in aversions to previously eaten foods (*2*). This ability to form associations between ingestion and subsequent illness (*3*) is probably responsible, in part, for the avoidance by rats of slow acting poisons (*2*). However, another factor must also be involved. Since rats are likely to eat a number of foods over a long period of time, there must be a mechanism by which they can associate the poisoned food with the effects of the poison. A poisoned food is bound to be novel; otherwise the rat would probably already be dead. Our hypothesis is that rats associate radiation sickness with novel food rather than familiar food if they have eaten both types before they become sick. Conventional conditioning procedures suggest that association of a stimulus with a consequence is likely to be inhibited if there has been a number of earlier presentations of the stimulus in the absence of that consequence (*4*). Furthermore, neophobia, the hesitancy with which rats approach novel foods (*5*), seems to indicate the existence of an investigatory reflex (*6*) to novel foods which may predispose rats to associate novel illnesses with them.

Forty-eight male Sprague-Dawley rats were housed in individual cages (Hoeltge HB-11A) throughout the experiment and were given continual access to water and to ground rat chow for 1 hour each day. During days 1 through 8, half the rats were made familiar with milk (equal parts of condensed milk and water, by weight) by being allowed to drink it for 5 minutes per day, 17 hours after they had eaten their meal of chow; the remainder of the rats were allowed to drink sucrose solution (19.7 percent by weight) under the same conditions. The rats ate these foods in test cages similar to the home cages, except that the test cages had provisions for recording the number of times each rat licked the spout.

The conditioning trial was administered on day 9. Half the rats under each familiarization condition were allowed 100 licks of the familiar food in one test cage; they were then immediately transferred to a second test cage, where they were permitted 100 licks of the other (novel) food (termed the f→n procedure). The remaining rats received the novel food prior to the familiar food (n→f). After they had eaten both foods the rats were returned to their home cages, from which the water bottles had been removed. After 60 to 70 minutes, half the rats exposed to each of the four previous combinations of treatments were x-irradiated and half were not, so that there were eight groups with six rats in each group. Radiation consisted of 50 roentgens received in the course of 21.3 seconds from a GE Maxitron 250 KVP unit at 30 ma, 250 kv, filtered through 1 mm of aluminum and 0.5 mm of copper. The control rats were placed under the unenergized x-ray unit. The rats were given water at their regular feeding time, about 4½ hours after they were irradiated, and it was available for the remainder of the experiment.

Conditioning was tested on day 12. Each rat was deprived of food for 15 to 18 hours and then was placed in the test cage for 30 minutes with free access to both the novel and the familiar food. Preference for the novel food was defined as the number of licks to the novel food divided by the total number of licks.

The irradiated rats showed a lower preference for the novel food than did the controls regardless of which earlier experimental procedures were used (Table 1). However this effect was not statistically reliable if only the rats for which milk was novel were considered. A probable reason is that there was a strong overall preference for sucrose, so that when milk was novel, the preference for it among the control rats was too small to permit a reliably smaller preference among the irradiated rats. Since rats prefer milk to grape juice (*7*), the procedure was repeated

Table 1. Mean preference for novel food: choice between sucrose and milk. An F test (novel food by conditioning sequence by irradiation) shows the following factors had reliable effects; novel food ($p < .001$), irradiation ($p < .01$), and irradiation by novel food interaction ($p < .05$). All other effects had $p > .25$. Because of the significant interaction, separate F tests were used to analyze the irradiation effect for each novel food; the irradiation effect was reliable when sucrose was novel ($p < .01$), but not when milk was novel ($p = .18$). Preference expressed as ratio between number of licks to the novel food and total number of licks.

Conditioning procedure	Preferences	
	Irradiates	Controls
	Novel food: sucrose	
f→n	0.534	0.948
n→f	.673	.904
	Novel food: milk	
f→n	.004	.036
n→f	.005	.015

Table 2. Mean preference for novel food: choice between grape juice and milk. The following effects were significant (F test): novel food ($p < .01$), irradiation ($p < .001$), and novel food by irradiation interaction ($p < .02$). All other effects had $p > .25$. The irradiation effect was significant when milk was novel ($p < .001$) but was marginal when grape juice was novel ($p < .08$). (In the context of the other results, this last probability, being two-tailed, may be considered evidence of reliability.) Preference expressed as in Table 1.

Conditioning procedure	Preferences	
	Irradiates	Controls
Novel food: grape juice		
f→n	0.056	0.119
n→f	.010	.109
Novel food: milk		
f→n	.052	.350
n→f	.026	.267

in a second experiment in which undiluted grape juice (Welch brand) was substituted for the sucrose solution used in the first experiment. In this second experiment, preference for the novel food was reliably lower among the irradiated rats regardless of which food was novel (Table 2). When saccharin and water are presented to the rats before they are irradiated, their aversion to these fluids is attenuated if these fluids are already familiar to them (*8*). Thus the greater associative strength of novel foods in our experiment appears to be a general principle of conditioning.

The rats exhibited neophobia in both experiments. During the conditioning trial, the rats tended to drink the novel fluid more slowly than the familiar fluid (Table 3) except when sucrose was novel; this exception may be attributed to the greater palatability of sucrose solution (Table 1). Furthermore, during the test day of each experiment, the preference for milk among the controls was reliably greater if it was familiar than if it was novel. In view of this prominent role of neophobia, the radiation effect reported here may have been obtained not because of any selective association of the novel food with radiation effects but because a history of illness increases neophobia. This possibility may be discounted because a novel food presented more than a day after x-irradiation will not be avoided (*9*). Thus the apparent role of neophobia is to enhance the association of unusual gastrointestinal events with previously ingested novel foods. How it does so is unknown, but one possibility may be discounted. The increased time with which the animal is usually in contact with the animal food probably is not responsible for the selective association of illness with it; when sucrose was novel, the rats showed the radiation effect even though most of them drank the sucrose as quickly as the milk. Furthermore, among the individual irradiated rats in this category, there was no correlation between the time they took to drink sucrose divided by the time they took to drink milk and the later preference which they showed for sucrose ($p > .25$, Spearman r).

Table 3. Proportion of rats requiring more time to drink the novel fluid than the familiar fluid on the day of conditioning (both experiments). Except when sucrose was novel, each proportion shown was reliably greater than the chance level of .500 ($p < .001$, sign test).

Novel food	Familiar food	Proportion
Sucrose	Milk	0.417
Milk	Sucrose	.958
Grape juice	Milk	.958
Milk	Grape juice	.917

The rats were not fed or given water from the time they ate the test foods until 6 hours later. Therefore, if any aftertastes were present while the illness began, the aftertaste of the food last ingested should have been stronger. If such aftertastes help rats associate what they have eaten with later illness, the aversion for the novel food should be greater under f→n procedure than under n→f procedure. The fact that our experiments did not show this result (Tables 1 and 2), together with other findings (*2*), seems to indicate that aftertastes are not primarily responsible for the ability of rats to associate ingestion with later illness.

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Visual Pathway Mediating Pineal Response to Environmental Light

Abstract. *Activity of the melatonin-forming enzyme, hydroxyindole-O-methyltransferase, in rat pineal is increased when the animal is exposed to continuous darkness, and it is decreased by exposure to continuous light. Response to environmental light is initiated in the retina and transmitted to the pineal by way of the central nervous system and the cervical sympathetics. The central visual pathway essential for mediation of this response is the inferior accessory optic tract. Visual pathways to thalamus and tectum do not participate in this response.*

The mammalian pineal gland contains a unique enzyme, hydroxyindole-*O*-methyltransferase (HIOMT), which transfers a methyl group of *S*-adenosylmethionine to the hydroxy group of *N*-acetylserotonin to form melatonin (*1*). Activity of this enzyme in rat pineal is controlled by environmental lighting. Synthesis of melatonin is depressed in animals kept in continuous illumination but increased in animals maintained in darkness (*2*). Information about environmental lighting is transmitted to the pineal from the retina by way of the brain and the sympathetic nervous system (*3*). In rats blinded by removal of both eyes the response to light by pineal HIOMT is lost, as is the response after denervation of the pineal by superior cervical ganglionectomy (*3*). Similarly, central lesions which bilaterally transect the medial forebrain bundle in the lateral hypothalamus produce a loss of the pineal HIOMT response (*4*). This suggests that a critical component of the central retinal projection is present either within or closely adjacent to the medial forebrain bundle. Anatomy of the retinal projection has been studied extensively in the rat (*5*). Axons of