Several other endocrine- and neuroendocrine-immune system interactions have been described (*1*), and these physiologic processes may be subject to or influenced by conditioning.

The present study does not provide direct evidence of conditioned immunosuppression, per se (for example, depressed autoantibody titers). Nonetheless, the results are consistent with previous data (*2*) indicating that the pairing of saccharin and cyclophosphamide enables saccharin, acting as a CS, to suppress immunologic reactivity; they are also consistent with the hypothesis that such conditioning might thereby delay the onset of autoimmune disease under a regimen of chemotherapy that was not, in itself, sufficient to influence the development of SLE in comparison with an untreated control group. As such, these findings constitute an elaboration of the biologic impact of conditioned immunopharmacologic responses. The present study suggests, further, that there is some heuristic value in analyzing a pharmacotherapeutic regimen in terms of conditioning operations. Based on the present paradigm in which conditioned stimulus presentations (placebo treatments) were substituted for some active immunosuppressive therapy, it may be hypothesized that the prescription of a noncontinuous schedule of pharmacologic treatment in contrast to an analysis of the effects of continuous regimens of drug (or placebo) would be applicable in the pharmacotherapeutic control and regulation of a variety of physiologic systems.

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22 September 1981; revised 24 December 1981

Endogenous Opiates and Energy Balance

Abstract. *Increasing the palatability of food has two opposite effects: it promotes overeating and provokes caloric output (energy expenditure). The increase in energy expenditure is too small to compensate for overeating and, as a result, obesity occurs. Repeated administration of zinc tannate of naloxone, a long-lasting opiate antagonist, completely abolishes this diet-induced obesity in rats. The drug accomplishes this not only by reducing overeating but also by increasing energy expenditure. This suggests that endogenous opioid peptides encourage obesity in two ways—by stimulating appetite for palatable foods and by reducing energy expenditures.*

In our Western societies the average adult gains about 13 kg between the ages of 20 and 50 years.

Certain animal species, such as rodents, follow a genetic program for an increase of adipose mass with age. This does not seem to be the human situation, since in non-Western societies average weight remains stable throughout adulthood and decreases slightly with old age. This has led to a general consensus that the weight gain observed in modern societies is essentially due to environmental conditions. The three main factors usually mentioned are the availability of a great variety of palatable foods, the decrease in energy expended, and the multiplication of stressors. That three factors usually occur together makes it difficult to appreciate their individual effects.

The only available experimental demonstration in human subjects concerns food choice. Replacing the usual varied meals by monotonous free feeding, in subjects whose physical activity and stressors are not modified decreases weight, which then stabilizes at a lower level (*1*).

Replacing a laboratory animal's usual monotonous laboratory food by a large choice of highly palatable items ("cafeteria" diet) induces overeating and an increase in weight (*2*, *3*). When cafeteria rats are given more exercise, their overweight is diminished, but not to the level of controls (*3*). Tail pinching, a stressor, provokes overeating, obesity, and an increase in plasma β-endorphin (*4*).

We hypothesized that the overavailability of various palatable foods acts, like a stressor, through the endogenous opiate system, which in turn modifies the two components of energy balance—intake and expenditure.

We have shown that short-term injections of opiate antagonists suppress hyperphagia both in genetically obese rodents (*5*) and in cafeteria rats (*6*). We now report that the repeated administration of a long-lasting opiate antagonist drug prevents obesity induced by the cafeteria diet by diminishing overeat-

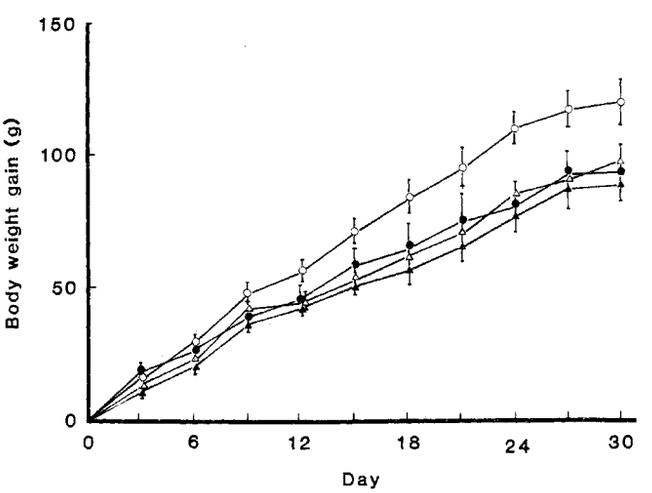

Fig. 1. Mean body weight gains. At day 30, the group given a cafeteria diet but no ZTN (○) had gained significantly more weight (analysis of variance, $P < .05$) than any of the other groups, none of which differed from each other. Symbols: ○, cafeteria-vehicle; ●, laboratory-food–vehicle; △, cafeteria-ZTN; and ▲, laboratory-food–ZTN.

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ing and increased energy expenditure.

Male Wistar rats (N = 104) weighing an average of 200 g were divided into four equal groups of equivalent weight. Two groups were allowed free access to laboratory food (M25). Animals in one of these groups were given intramuscular injections (1 ml per kilogram of body weight) of olive oil (vehicle); animals in the second were injected with zinc tannate of naloxone (ZTN) (5 mg/kg) in the olive oil vehicle. Injections were given every 3 days at 7:00 p.m., at which time the animals were weighed. Two cafeteria groups received in addition to the laboratory food and injections four highly palatable food items, which were changed every day at 7:00 p.m. The rats were kept in individual cages throughout the experiment. Temperature was maintained at 23° ± 2°C, and lights were turned on for 12 hours each day beginning at 7:00 p.m.

As expected (*2, 3*) the rats receiving a cafeteria diet gain more weight than those receiving laboratory food (Fig. 1). Cafeteria rats receiving ZTN, however, exhibited ponderal curves similar to those receiving laboratory food. It seems that ZTN acted specifically on the weight of the obese animals, since it did not significantly modify the ponderal curves of rats given laboratory food. This result is consistent with those of Recant (*7*) with repeated injections of naltrexone; Brands (*8*) reported steep weight loss during 2 days, but with a dose of ZTN four times as strong. The weight gain inhibiting action of ZTN in cafeteria rats resembled that obtained in obese *ob/ob* mice treated repeatedly with naltrexone (*7*). Thus, in two models of obesity, one purely genetic, the other purely nutritional, opiate antagonists countered the overweight.

The food intake of cafeteria rats, expressed in terms of energy, was significantly higher than that of laboratory food rats throughout the experiment (Fig. 2), which is consistent with previous results (*2, 3*). In rats fed laboratory food, ZTN slightly decreased food intake. In the cafeteria rats, ZTN decreased food intake; the cafeteria-induced hyperphagia was reduced approximately by half, but they still consumed more than the two groups receiving laboratory food. This raises the question of why, with a higher food intake, the ZTN cafeteria animals gained no more weight than those receiving laboratory food. The answer can be found in the results of energy expenditure.

Oxygen consumption measured for 1 hour in resting animals (*9*) in a closed underwater circuit respirometer at 29°C was significantly higher in cafeteria rats (mean ± standard error of the mean, 17.09 ± 0.46 J/hour per square centimeter of surface area) than in rats fed laboratory food (15.55 ± 0.21, F = 9.0, $P < .005$). Our result confirms that of Rothwell and Stock (*10*) and is consistent with the general feature of energy balance: overeating increases energy expenditure, and a restricted diet decreases it (*11*). Treatment with ZTN increased oxygen consumption by both groups of rats (cafeteria, to 19.52 ± 1.04, F = 22.21, $P < .005$; laboratory food, 17.47 ± 0.25, F = 13.79, $P < .005$). Motor activity was not measured, but no identifiable behavioral changes were noted.

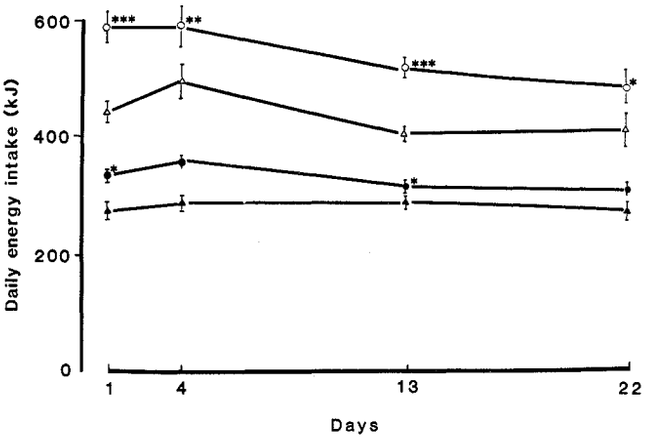

Fig. 2. Mean daily energy intake of rats allowed free access to laboratory food (filled symbols) or cafeteria diet (open symbols), treated with vehicle (circles) or ZTN (triangles) (5 mg/kg). Food intake was estimated from the weight of laboratory food and the weight of each cafeteria food item consumed; energy intake was then calculated through the use of Atwater's coefficients (*16*). Statistical comparisons were made with F tests between the two ZTN groups and their respective vehicle control groups. *, $P < .05$; **, $P < .025$; ***, $P < .005$. A significant difference between cafeteria-ZTN and laboratory-food–vehicle groups was found in all cases ($P < .005$).

We know of no data in the literature about the role of opiate antagonists on energy expenditure. In a previous unpublished experiment, we studied oxygen consumption after a single injection of naltrexone at a dose (*6*) that suppresses for 3 hours hyperphagia induced by the cafeteria diet; naltrexone had no effect on oxygen consumption.

The discrepancy between the short- and long-term effects of naltrexone and ZTN suggests that opiate antagonists do not act directly on oxygen consumption. Some points of similarity can be established between the increase of energy expenditure observed with ZTN and two other energetic phenomena related to the opiate system: opiate antagonists stop hibernation (*12*), thus increasing energy expenditure; β-endorphin injected intraventricularly provokes hypothermia (*13*). On the basis of these two facts, Margules (*14*) hypothesized that one role of the endogenous opiate system could be to spare energy. In our cafeteria group, the actual energy expenditure was a compromise between two antagonist forces: (i) the increase provoked by overeating or overweight and (ii) the decrease provoked by excess β-endorphin. The compromise is in favor of overeating or overweight in such a way that the energy expenditure is increased. The ZTN partially cancels the decrease in oxygen consumption caused by β-endorphin and leads to a net increase in energy expended. The combination of increased energy expenditure and decreased food intake prevents obesity.

The endogenous opiate system is not indispensable for an adequate control of food intake in a predictable environment—for example, with monotonous food—but it becomes active when the reward system is disrupted—as with an unavoidable stress, a forced fast, or a multiplication of desirable selections. With human obesity there is no reason to believe that the β-endorphin system is always active, since in many instances, obesity is not provoked by hyperphagia. When hyperphagia does exist, however, whether it be related to genetic [as in the Prader-Willi syndrome (*15*)] or to environmental factors (overresponsiveness to a cafeteria life-style called externality), the endogenous opiate system is likely to be involved.

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13 July 1981; revised 13 October 1981

Chromatic Valence Curves: Alternative Interpretation Derived by the Direct Matching Method

Abstract. *The amount of red chromatic valence of the red-green opponent colors channel of the human visual system has been reported to be greatly reduced in short wavelengths when the hue-matching method is used to measure red valence instead of the more typical cancellation method. Receptive fields with a silent surround were postulated to explain the reduction, and it was emphasized that the reduced valence curve represented the true chromatic valence curve of the visual system. In the present studies the previous results are interpreted to be a direct consequence of the method and the particular matching stimuli used. It is shown that the reduction can be explained by the existing color-matching data without appealing to the silent surround hypothesis.*

A new method was introduced by Ingling *et al.* (*1*) to measure the chromatic valence curves of the opponent-colors theory (*2*) which Ingling *et al.* claim to be superior to the usual cancellation method in that the new method reveals true amounts of the chromatic sensations. The new method, which is called the direct hue-matching method, entails matching the hue of a test stimulus with a mixture of two primaries. For example, if one is interested in obtaining the red chromatic valence of a 450-nm light in the short wavelength region of the spectrum, the 450-nm light is juxtaposed in a split field with a mixture of a blue primary of 480 nm and a red primary of 680 nm. The amounts of red in both fields are equated by adjusting the radiances of the primaries. The red chromatic valence is given by the amount of the red primary in the mixture.

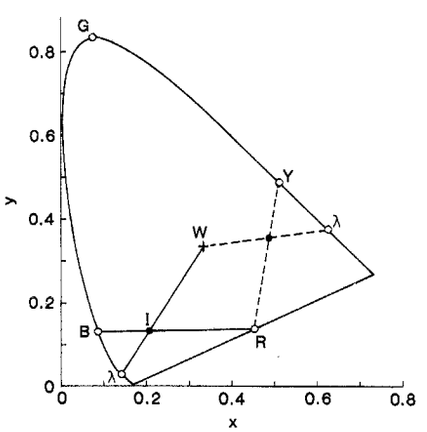

Fig. 1. Scheme to explain the hue-matching method.

Using this method, Ingling *et al.* (*1*) observed a great reduction of the red chromatic valence in the violet region of the spectrum when compared with that obtained by the cancellation method. To explain the difference Ingling *et al.* postulated a silent surround receptive field in which the inhibitory surround becomes effective only when the excitatory center is active, the situation which prevails in the cancellation method. According to their hypothesis, the red chromatic valence at short wavelengths is overestimated in the cancellation method in which the silent surround becomes active to reduce the effectiveness of the green canceling light.

Although the hypothesis is attractive and is helpful in searching for color vision mechanisms in human subjects, we have another interpretation of the results, one which does not require such a hypothesis. From the data of Ingling *et al.* one cannot ascertain the subject's "end point" in the experiment when the relative radiances of the primaries were adjusted. The expression "hue matching" was used, which suggests that the subject achieved a hue match between the test stimulus and the mixture of primaries in spite of the difference in their saturation. However, the expression "same amount of redness" was also used, which suggests that the subject equated the absolute amount of redness in the mixture of 480 nm and 680 nm to that in the test stimulus of 450 nm, for example, in determining its red chromatic valence. The luminance of both fields was kept at 100 trolands. However, these two expressions define, at least in principle, quite different criteria. In determining an equal amount of redness the subject would disregard the amount of blueness in the fields and concentrate only on the amount of redness. The hue of two fields might differ considerably in overall appearance while assuring the same amount of redness. In hue matching the subject would concentrate on reaching the same balance between redness and blueness in the mixture as that in the test stimulus.

With an experimental setup similar to that of Ingling *et al.* (*1*), we asked subjects to adjust the mixture of radiances in experiments that used both criteria. A test stimulus of wavelength 420 nm was matched with the mixture of 680 nm and a short wavelength that corresponded to the unique blue detected by each subject. All five subjects participating in the experiment found it easy to use the hue-matching criterion. Four of the subjects, however, found it impossible to achieve

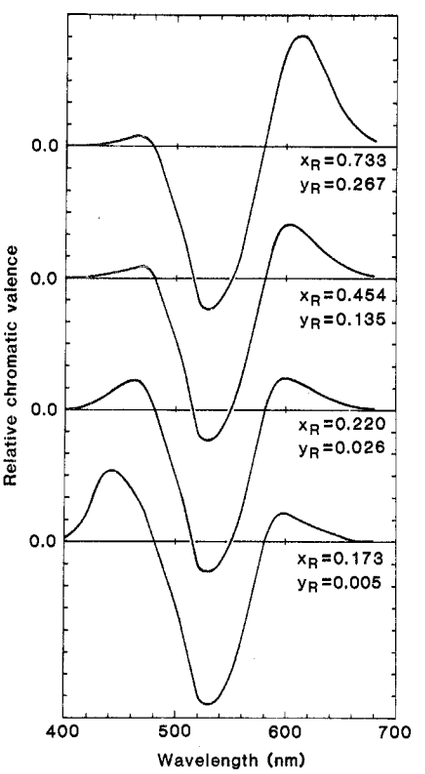

Fig. 2. Red-green chromatic valence curves derived by calculations based on hue matching with various red primaries (x_R, y_R).

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