difference between the two classes was well defined by the third week of feeding. Initially, the short-lived rats preferred diets significantly lower in protein content than those selected by the long-lived rats. At approximately 7 weeks of age, the tendency to select diets of lower protein/carbohydrate ratio was reversed. Beyond age 200 days they selected diets containing even higher levels of protein than those chosen by the long-lived rats.

The diets chosen by young animals not subjected to bias appear to have a physiological basis (*7*), but with regard to longevity, the selections confer an advantage for only some of the rats; for others the selections are associated with short lifespans. Regardless of the quantity or composition of the diet selected, the frequency of several age-related diseases is uniformly high (*2*). Individual appetite specificity notwithstanding, there are dietary regimens that are conducive to an extension of life-span (*1, 3, 8*) and reduction in suseptibility to some age-related diseases (*2, 3, 9*). However, there seem to be limits to the age period during which dietary manipulation will evoke such responses (*10*). Some imposed regimens that exert an appreciable life-prolonging influence when begun at an early age may drastically curtail duration of life if delayed until midlife. There are also temporal limitations under free choice conditions in that there are distinct time differences with regard to when and to what degree a dietary factor correlates with length of life.

The number of dietary choices open to the rat was limited in this study. Even so, a substantial proportion of the variation in life-span among animals has been explained solely by the appetite for carbohydrate and protein. It is likely that an even larger proportion of the variance would have been accounted for had the rats been permitted to express their choice for other essential nutrients. If such choices also contribute to an extension or curtailment of life, dietary practices early in life may provide a critical measure for estimating the life-span of an individual.

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4 November 1975; revised 2 June 1975

Satiety: A Graded Behavioral Phenomenon Regulating Caloric Intake

Abstract. *Rhesus monkeys inhibited their feeding in response to intragastric nutrient preloads, so as to maintain a constant caloric intake. There is a definite dose-response relationship to calories which does not depend on the volume, caloric concentration, or nature of the nutrient. This accurate control is accomplished even though some of the preload remains in the stomach throughout the feeding period.*

The concept of satiety has been the subject of much theoretical consideration in feeding control, but until recently only modest experimental study has been directed toward it. Thus, a disturbance in satiety has long been proposed as an explanation for hypothalamic hyperphagia (*1*), and the ventromedial hypothalamic (VMH) region has been proposed as the "satiety center." However, recent experimental results have challenged these proposals by showing that hyperphagic animals with VMH lesions seem just as capable as normal animals of inhibiting feeding in response to nutrient. Studies in the rat have employed intragastric (*2*), intravenous (*3*), and intraperitoneal (*4*) nutrient preloads to demonstrate this capacity. We

Table 1. The effect of intragastric nutrient preloads on caloric consumption. The total column under the experimental condition is calculated by adding the caloric value of the preload to the meal calories. All results are expressed as mean ± standard error of the mean. *N*, number of experiments; glu, glucose; B.N., balanced nutrient; sta, starch; cas, casein. Numbers of groups of experiments, total number of experiments, and means (± S.E.M.) of groups of experiments and of the total are printed in italics.

N	Control condition	Experimental condition			
	Meal (kcal)	Preload (kcal)	Meal (kcal)	Reduction from control (kcal)	Total (kcal)
5	489 ± 10	75 (glu)	422 ± 15	68.5 ± 6	497 ± 17
6	451 ± 14	150 (glu)	305 ± 21	148 ± 15	454 ± 21
8	437 ± 15	150 (B.N.)	273 ± 22	164 ± 13	423 ± 22
6	454 ± 24	150 (sta)	305 ± 23	150 ± 7	455 ± 23
6	438 ± 26	150 (MCT)	282 ± 25	156 ± 16	432 ± 25
6	418 ± 8	150 (cas)	251 ± 24	167 ± 17	401 ± 24
32	*439 ± 7*			*157 ± 4*	*432 ± 11*
7	442 ± 13	300 (B.N.)	134 ± 15	306 ± 18	434 ± 14
6	447 ± 19	300 (sta)	156 ± 21	291 ± 19	456 ± 21
6	461 ± 16	300 (MCT)	156 ± 29	304 ± 17	456 ± 29
6	461 ± 15	300 (cas)	159 ± 14	302 ± 20	459 ± 14
25	*452 ± 5*			*301 ± 3*	*451 ± 6*
5	446 ± 22	450 (B.N.)	38 ± 12	408 ± 25	488 ± 12
67	*449 ± 2*				*448 ± 3*

have reported (*5*) that both normal and hyperphagic primates (rhesus monkeys) were able to inhibit subsequent food intake to at least one form of gastric nutrient preload in a fashion that appeared to regulate caloric ingestion during feeding periods equally well in the two groups.

The regulation of caloric intake through a satiety mechanism has been suggested. Booth and others (*6*) have shown in rats that the reduction in intake in response to a gastric glucose load corresponded to the caloric value of the carbohydrate supplied. Further examination of the natural phenomenon of satiety defined as the inhibition on feeding provoked by food itself is needed to examine the accuracy of regulation and the influence of different nutrients in the control process.

Below we report the inhibition of daily feeding provoked by a variety of intragastric preloads in the rhesus monkey (*Macaca mulatta*) and demonstrate that this animal can control its feeding with such remarkable accuracy that daily caloric ingestion can be rigidly controlled despite differences in the nutrient character, the volume, or the caloric concentration of intragastric contents.

The experimental animals were five male monkeys weighing 4 to 5 kg. They were housed in individual cages and fitted to a light leather vest onto which was attached a multiflexible stainless steel cable. A Silastic cannula, 0.062 inch in inside diameter by 0.125 inch in outside diameter (1 inch = 2.54 cm), was implanted into the lumen of the stomach with a Silastic button sewn into the gastric wall. The cannula was exteriorized between the shoulder blades, passed through the cable, and brought outside the cage. The animals restrained in this manner were able to range freely within their cages, and their feeding quickly returned to preoperative levels.

The animals were trained to consume their daily food within a 4-hour feeding period. The food was Purina Monkey Chow (4.18 kcal/g, by bomb calorimeter). They were always given enough food to ensure that there would be some remaining at the end of the feeding period. The leftover food was collected and amount eaten calculated. Water was always available to the animals. The animals maintained their body weight throughout our study.

Through the Silastic cannula, preloads of nutrient or equivolumetric saline were infused 15 minutes before the 4-hour feeding period. The nutrient preloads were one of the following: a balanced mixture of fats, carbohydrates, and proteins, made from commercial liquid diets (Dyne, Biolab Corp., and SMA, Wyeth Laboratories); two carbohydrate solutions, glucose and cornstarch; a lipid, median chain triglyceride oil (MCT, Mead Johnson); and a protein solution, casein hydrolyzate enzymatic dissolved in saline. With the exception of the MCT and glucose the preloads were given in constant volume of 150 ml. The MCT (7.66 kcal/ml) and glucose (0.75 kcal/ml) preloads were each given at constant caloric concentration, the volume of these preloads being determined by the total calories to be delivered. Nutrient preloads were preceded and followed by a day on which the animals received an equivolumetric saline preload. The difference between the amount of food eaten on the day when the preload was a nutrient and the mean amount of food eaten on the saline preload days preceeding and following was taken as the reduction in feeding provoked by the nutrient preload.

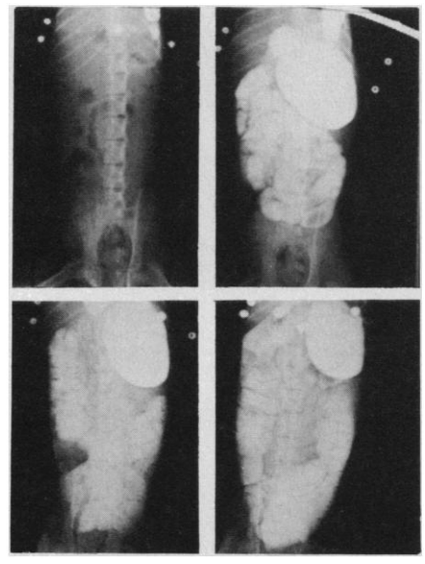

Fig. 1. The movement of balanced nutrient preload (150 ml; 1 kcal/ml) in the gastrointestinal tract. (Top left) Prior to preload. (Top right) Five minutes after preload. Nutrient in stomach and small bowel. (Bottom left) One hour after preload. Nutrient in stomach and small and large bowel. (Bottom right) Four hours after preload. Nutrient still remaining in the stomach.

As shown in Table 1, feeding is inhibited with every nutrient preload. The accuracy of inhibition when the feeding is expressed in calories is remarkable. The reduction of feeding provoked by any preload is within 10 percent of the caloric value of the preload in all but the 150-kcal protein infusion. That this variation may be accountable to chance fluctuations between days rather than to any inaccuracy of caloric regulation is demonstrated by the observation when all 67 experiments are combined. The mean total calories taken in with saline preloads and the mean total calories with nutrient preloads differ by one calorie. There is no tendency for animals to under- or overcompensate for the calories in the preloads. There is a definite dose-response relationship to calories. This dose response does not depend on the volume of preloads, since this was constant at 150 ml for the balanced nutrient, starch, and casein, and it does not depend on the caloric concentration of the preloads, since this was held constant for glucose and MCT.

Only at the 450-kcal preload level is a result observed that might be considered a reduction in the inhibitory capacity of calories in the preload. But total calories in this preload were slightly more than the mean calories eaten in the control saline infusion situation. Thus, in this condition it is impossible to detect accurate compensation for the preload because animals cannot eat less than nothing in the meal that follows it. Actually, some of the monkeys ate nothing in the 4 hours after these preloads, while others ate a few grams of food. In addition, monkeys were able to inhibit thier meals accurately after the 75-kcal preload even though this caloric amount approaches the range of the normal day-to-day variation in meal size.

As designed, these experiments permit some consideration of the mechanisms mediating the satiety influence. By demonstrating such accuracy of inhibition to intragastric preloads, we can say that taste, olfaction, and swallowing are not essential to satiety in the primate. Second, plasma glucose levels were measured during a 4-hour period following several preloads during which the animals were not allowed access to food. There was a prompt rise with the balanced nutrient and starch, reaching a peak within 15 minutes and remaining above baseline levels throughout the 4 hours. However, the MCT oil did not produce a rise but actually led to a gradual decline, with the level after 4 hours at about half (28 mg per 100 ml) of the baseline level (60 mg per 100 ml). While all three preloads were capable of provoking satiety with accurate caloric regulation, they did not influence plasma glucose in the same manner. This indicates that, although plasma glucose elevation may be a sufficient means for the mediation of satiety, it is not a necessary step in the train of events and there must also be other mechanisms.

We have followed the 150-kcal balanced nutrient by x-ray through the gastrointestinal tract by adding to it 10 ml of a water-soluble radiopaque substance (Gastrografin, Squibb). As shown in Fig. 1, although the preload entered the small bowel promptly on its infusion, a sizable amount remained in the stomach throughout the 4-hour feeding period. It is intriguing that

nutrient still in the stomach and thus presumably not entered into energy metabolism nonetheless can effectively control feeding so that the animal compensates accurately for the energy content of this yet to be absorbed nutrient.

Satiety cannot simply be a response to volume or caloric concentration in the preloads, since we have controlled for these features individually and found them not crucial. Presumably an integration of several mechanisms, including the capacity to monitor calorie concentration and gastric distention, is active here. Liebling *et al.* (*7*) have shown in rats with gastric fistulas that a small amount of nutrient infused directly into the duodenum will effect a transient inhibition of ongoing intake. Sharma and others (*8*) have demonstrated that gastric distention alone is sufficient to inhibit intake on a short-term basis and reported the existence of stretch receptors mediated by vagal afferent fibers. Hunt and Stubbs (*9*) have reported that in humans gastric emptying time is directly related to caloric concentration and postulated the existence of "energy receptors" within the small bowel. Thus, there is evidence for the existence of mechanisms which can monitor the nature and volume of nutrient present within the gastrointestinal tract.

These mechanisms and perhaps others in liver (*10*) and brain (*11*) must function with close integration, as our results demonstrate that satiety is the behavioral outcome of a regulatory system capable of monitoring and controlling caloric ingestion. This system can be of such accuracy as to rival that of the controls on the vital autonomic functions such as blood pressure and respiration. The existence of such an accurately graded phenomenon for the control of caloric ingestion in primates raises questions as to how such a system operates in relation to available body stores, questions that are pertinent to such conditions as hypothalamic hyperphagia and the human disorders of obesity and anorexia nervosa.

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12. This work was supported by PHS grant 1 RO1 AM 18554-01 and the General Research Fund, University of Oregon Health Sciences Center.
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16 June 1975

Sexual Inhibition Is Reduced by Rostral Midbrain Lesions in the Male Rat

Abstract. *Electrolytic lesions in a circumscribed area of the rostral midbrain of rats shortened the inhibitory period following ejaculation, thereby increasing the number of ejaculations achieved in 1-hour tests. These lesions also interrupted the dorsal norepinephrine bundle as reflected in a 63 percent reduction in telencephalic or cortical norepinephrine.*

Most contemporary theories dealing with central nervous system regulation of sexual behavior of male mammals postulate the existence of inhibitory neural processes which interact with excitatory mechanisms in producing the distinctive species-typical copulatory pattern (*1*). While the bases for such hypotheses are largely indirect and subject to alternate interpretations, one feature of the copulatory pattern that has been most widely cited as reflecting inhibitory processes is the postejaculatory interval, a prolonged period of sexual inactivity and unresponsiveness to the female which follows ejaculation. In the rat, the species studied most extensively, little information exists regarding the location or nature of the postulated inhibitory mechanisms. In one study, large midline lesions, destroying a poorly identified area at the junction of the diencephalon and mesencephalon, produced accelerated copulatory performance, including an attenuation of the postejaculatory interval (*2*). However, attempts to localize the effective site have thus far led to inconsistent results (*3*).

In the course of our investigations into the contribution of ascending catecholamine systems to the normal expression of male copulatory behavior, lesions were made to disrupt the dorsal norepinephrine (DNE) bundle before it descends into the hypothalamic medial forebrain bundle (*4*). Our results indicate that bilateral destruction of a circumscribed area (see Fig. 1) within the rostral midbrain region through which the DNE bundle projects (*4*) reliably shortens the postejaculatory interval to the extent of increasing the number of ejaculations achieved in 1-hour tests.

Sexually experienced male Long Evans rats (300 to 350 g) were given a minimum of three preoperative and four postoperative mating tests of 1-hour duration, spaced at 10-day intervals. Tests were conducted during the dark phase of a reversed 12-hour-light, 12-hour-dark cycle. Males were tested with ovariectomized, estrogen- and progesterone-treated females previously screened for sexual receptivity.

Thirty-one males received bilateral, electrolytic lesions (*5*) aimed at interrupting the DNE bundle at the rostrocaudal level of the interpeduncular nucleus. At this level the DNE bundle shows maximum separation from the other biogenic amine–containing pathways (*4*). Six males served as unoperated controls and nine underwent the sham procedure in which an electrode was lowered to a point 5 mm below the surface of the skull and then withdrawn.

The dramatic and unexpected change in some measures of copulatory activity obtained with the first five lesioned animals led us to replicate the experiment three times over a period of 24 months. Lesioned rats in each replication showed a significant mean increase in ejaculation frequency (ejaculations per test) relative to all controls ($P < .001$ in each case, by t-test). The effect was confirmed by a chi-square analysis.

Subsequently, as a means of determining whether some lesions might be more effectively placed than others, the following classification method was employed. Two rats were selected that showed substantial increases in ejaculation frequency and were used as "criterion rats" for histological grouping, preliminary to statistical analysis. Their brains were serially sectioned and stained by the Weil method. Composite, bilaterally symmetrical maps of lesion location were constructed for several rostrocaudal planes corresponding to the König and Klippel atlas (*6*) and spanning the combined longitudinal extent of lesions in both animals. These maps, which represented only the areas of destruction