# Satiety Signals

MORTON I. GROSSMAN, M.D., PH.D.*

THE TITLE of this paper is a concession to brevity; a more exact one might read "Effects Produced by Eating which Inhibit Further Eating." Satiety is defined as an affective (hence, psychic) state brought on by eating and characterized by lack of desire to eat. So defined, it is subject to study only in man and only by interrogation. This paper deals with the behavioral correlate of satiety, cessation of eating. The study is based on observations on feeding behavior in animals, and it is doubtful whether inferences about the psychic state of satiety can be made from such data. Presumably, but not necessarily, when a man or animal stops eating while more food is available, he experiences satiety.

Eating leads to cessation of eating. What are the mechanisms of this effect? By fractionating the process of eating and its sequelae into stages, an assessment can be made of the contribution of various factors to the effect on cessation of eating.

## SHAM FEEDING

Analysis of the fractionated feeding process begins with a consideration of sham feeding, in which the food eaten is diverted to the outside of the body through an esophageal fistula and thus is prevented from entering the stomach. In dogs so prepared the eating process is remarkably altered. Janowitz and Grossman[1] found that dogs whose mean duration of eating had been 2.5 minutes before making the esophageal opening ate for a mean of 14.1 minutes in the first sham feeding test to which they were subjected. Not only was duration of eating greatly prolonged in any one test, but this prolonged eating could be repeatedly demonstrated at short intervals. A second sham feeding test, an hour after the first one, lasted as long as the first test, and this process could be repeated hour after hour. Clearly, passage of food through only the mouth and pharynx is relatively ineffective in producing cessation of eating and the cessation so produced is shortlived.

What happens when an attempt is made to synthesize the normal eating process by placing food in the stomachs of dogs with esophagostomies? Some experiments by Share et al.[2] are summarized in Figure 1. Two effects are demonstrated. First, duration of sham feeding eighteen hours after the last intragastric feeding is inversely related to the size of the intragastric feeding. This effect occurs only after a period of equilibration over a number of days and is related to phenomena which will be considered later. Second, duration of sham feeding is reduced by an immediately preceding intragastric feeding. Because of interaction between the first and second effects the exact quantitative relations of the second effect is not certain. Specifically, it is not known whether a dog with an equilibrium of energy will show an exactly compensatory decrease in sham feeding as the result of an immediately preceding or simultaneous intragastric feeding. The next series of studies, on intragastric feeding in intact dogs with gastric fistulas, relates to this question.

## INTRAGASTRIC FEEDING

Figure 2 presents data gathered by Janowitz and Grossman.[1] When about one fifth of the mean amount of food eaten during a long control period was placed directly into

From the Wadsworth Veterans Hospital and Departments of Medicine and Physiology, University of California, Los Angeles, California.

* Chief, Gastroenterology Section, Veterans Administration Hospital; Clinical Professor of Medicine and Physiology, University of California at Los Angeles.

Present address: Veterans Administration Center Los Angeles, California.

Presented at the Brook Lodge Invitational Symposium on Energy Balance, sponsored by The Upjohn Company, September 29, 1959, at Brook Lodge, Augusta, Michigan.

the stomach twenty minutes before feeding, no significant reduction in food intake occurred. When the fraction placed in the stomach was one-half the mean control intake, an apparently fully compensatory decrease was seen. A non-nutritious bulk substance (karaya gum gel) produced an effect indistinguishable from that of food. When the interval between intragastric feeding and offering food was increased to four hours, no depression of intake resulted. The results of this set of experiments suggest: (1) the threshold for detection of inhibition of oral feeding by intragastric feeding lies between one fifth and one half of the usual meal size; (2) inert bulk is as effective as food in producing inhibition, thus, a major signal for cessation of eating is elicited by gastric distention; (3) food which has emptied from the stomach does not produce inhibition. This last conclusion is valid only for short-term observations. These conclusions are based upon relatively few observations; the subject would repay more detailed study to establish the quantitative relations more clearly.

In addition to distention, another mechanism operating from the upper gastrointestinal tract which might be expected to influence feeding is the hormone, enterogastrone. Since this hormone inhibits gastric contractions and since the presence of gastric contractions is one of the indices of the hunger state, inhibition of these contractions by enterogastrone could be expected to be associated with inhibition of feeding. Janowitz and Grossman[3] tested this hypothesis in a study summarized in Figure 3. Prefeeding small amounts of sucrose or cream, amounts known to be capable of stopping gastric contractions by release of enterogastrone,[4] did not alter the amount of food eaten. Larger amounts of sucrose or cream were effective but this could be ascribed to gastric distention. These results suggest that enterogastrone does not play a role in regulation of food intake, but, as will be pointed out later, negative experiments are seldom crucial.

## BLOOD LEVEL OF NUTRIENTS

The level of nutrients in the blood is increased

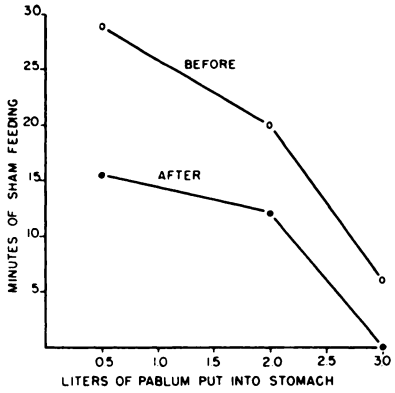


FIG. 1. Relation between size of intragastric feeding and duration of sham feeding. The upper line, labeled before, refers to tests performed before the last intragastric feeding. The lower line, labeled after, refers to tests performed immediately after intragastric feeding of the indicated amounts. Values are means of three dogs. (Data from: SHARE, L., MARTYNIUK, E. and GROSSMAN M. J. *Am. J. Physiol.*, 169: 229, 1952.[2])

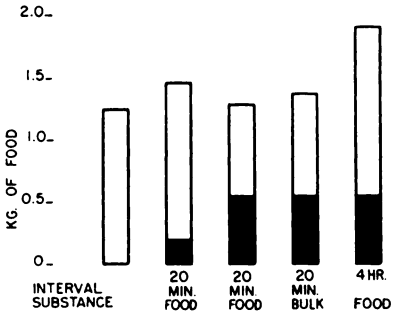


FIG. 2. Effect of putting substances in stomach on food intake immediately thereafter. Values are means for three dogs. Open bars represent oral food intake, black bars intragastric feeding. (Data from: JANOWITZ, H. D. and GROSSMAN, M. I. *Am. J. Physiol.*, 159: 143, 1949.[1])

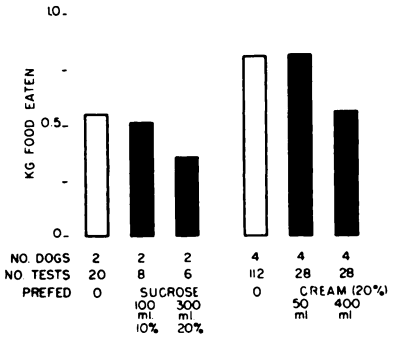


FIG. 3. Effect of prefeeding sucrose solution or cream immediately before offering regular food to dogs. (Data from: JANOWITZ, H. D. and GROSSMAN, M. I. *Am. J. Physiol.*, 164: 182. 1951.[3])

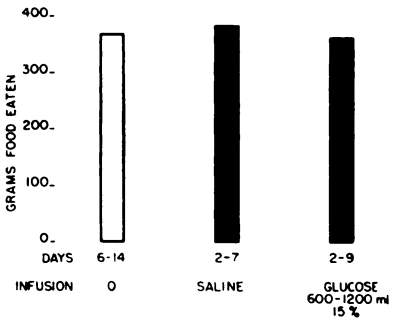


FIG. 4. Effect of intravenous infusion of glucose solutions on oral food intake in dogs. Mean values for five dogs. Number of days refers to number of consecutive days infusions were continued. (Data from: JANOWITZ, H. D., HANSON, M. E. and GROSSMAN, M. I. *Am. J. Physiol.*, 156: 87, 1949.[5])

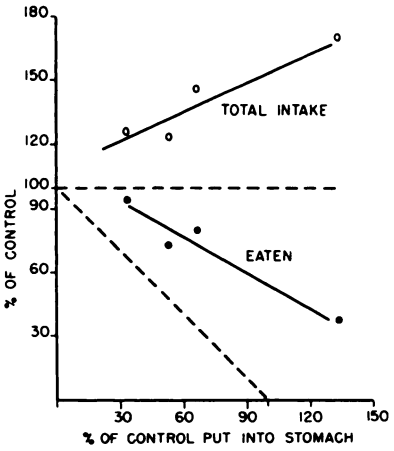


FIG. 5. Effect of various levels of intragastric feeding on oral food intake. Mean values for four dogs for the first two weeks of intragastric feeding. Sloping dotted line is the expected oral intake if oral plus intragastric feeding were to equal the control value. (Data from: SHARE, I., MARTYNIUK, E. and GROSSMAN, M. I. *Am. J. Physiol.*, 169: 229, 1952.[2])

while these nutrients are being absorbed from the gut. It might reasonably be anticipated that these elevations would play a role in regulation of food intake. A direct test of this hypothesis is the study of the effect of intravenous infusion of nutrients on food intake. Glucose is the only nutrient which has been extensively studied in this way. Figure 4 summarizes a portion of the data from a study by Janowitz et al.[5] Intravenous administration of large amounts of glucose immediately before feeding did not depress food intake. Similar negative results were

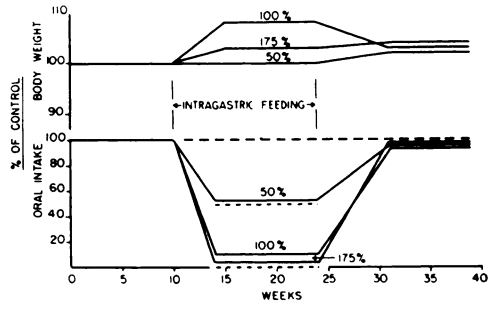


FIG. 6. Body weight and oral food intake of dogs during prolonged intragastric feeding at various levels. Percentage numbers refer to level of intragastric feeding as per cent of control oral intake. Dotted lines indicate expected oral intake if exact compensation for intragastric feeding occurs. Mean values for three dogs. (Data from: JANOWITZ, H. D. and HOLLANDER, F. *Ann. New York Acad. Sc.*, 63: 56, 1955.[7])

obtained by Bernstein and Grossman[6] in studies with both intravenous and intragastric administration of glucose to human subjects. Other aspects of the glucostatic theory of regulation of food intake are considered by other participants of this symposium. Our observations do not support the theory, nor do they disprove it.

## THE POST-ABSORPTIVE STATE

The final step in the fractionation of the feeding process is a consideration of the post-absorptive state, the effect of nutrients which have left the digestive tract and the blood. This can be conveniently studied by intragastric feeding performed many hours before oral feeding is measured. Figure 5 is derived from data published by Share et al.[2] During the first two weeks of daily intragastric feeding the depression of oral feeding was not fully compensatory; the sum of intragastric and oral feedings far exceeded the control oral intake which presumably represents the requirement for energy balance. More prolonged studies of this type were performed by Janowitz and Hollander[7] and are summarized schematically in Figure 6. During the initial four weeks of intragastric feeding oral intake progressively decreased until it reached the expected level and thereafter remained at that level while intragastric feeding was continued for ten more weeks. With cessation of intragastric feeding the length

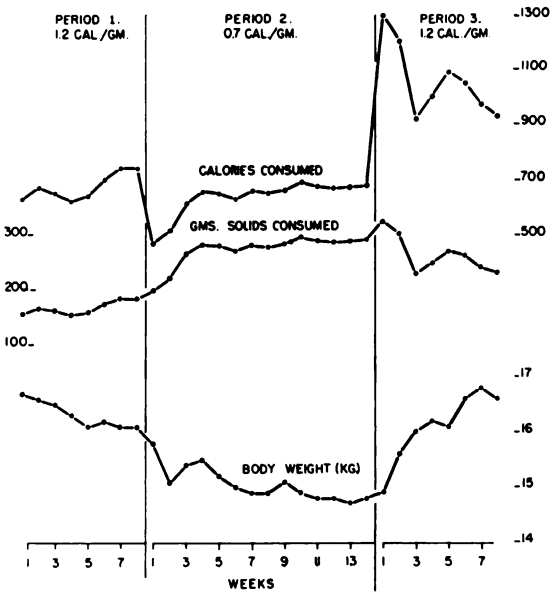


FIG. 7. Effect of change in caloric density on oral food intake and body weight Mean value for six dogs. During period 2 the regular dog food was diluted with hydrated cellulose. (Data from: JANOWITZ, H. D. and GROSSMAN, M. I. *Am. J. Physiol.*, 158: 184, 1949.[1])

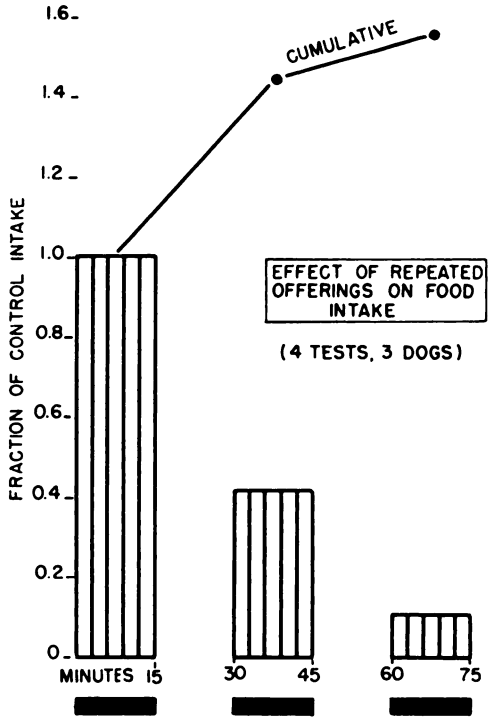


FIG. 8. Food intake during three successive fifteen minute offerings separated by fifteen minute periods of removal of food. The black bars designate periods when food was offered. Comparison is with control period when food was offered once daily for forty-five minutes. (Data from: SHARE, I. and GROSSMAN, M. I. Unpublished data.[10])

of time required for equilibration to be re-established to the original level of intake was even longer, an average of seven weeks. During these periods of equilibration at the onset and offset of intragastric feeding the dogs received large excesses of calories. In the dogs receiving 175 per cent of control intake intragastrically, this caloric excess occurred throughout the intragastric feeding period as well. And yet, *mirabile dictu*, increases in body weight were barely detectable. This is similar to the observation of Fenton et al.[8] who found that certain strains of mice did gain weight when they consumed extra calories as a result of being placed on a high fat diet. When positive energy loads are induced in dogs by intragastric feeding, a long period of time (weeks) is required before equilibration of oral intake occurs.

Variation of the caloric density of the diet produces an analagous situation with negative energy loads. Figure 7 summarizes data reported by Janowitz and Grossman.[9] After equilibration on a regular diet, dogs were fed food diluted with cellulose. Again it will be noted that equilibration at the start and end of feeding of the diluted diet required many weeks.

From the observations thus far presented the following working hypothesis can be derived. Food is metered in the mouth, pharynx and stomach. The nature of the detectors in these areas is not known, but volume appears to be of great importance and hence distention receptors can be postulated. When the signals to the brain from these detectors reach a certain level feeding reflexes are inhibited; eating ceases. The setting of this mechanism is probably determined by energy balance. This setting displays considerable inertia; the volume of food ingested tends to remain constant and only changes slowly in response to positive or negative energy loads. How the energy loads influence the setting, how the tissues tell the brain

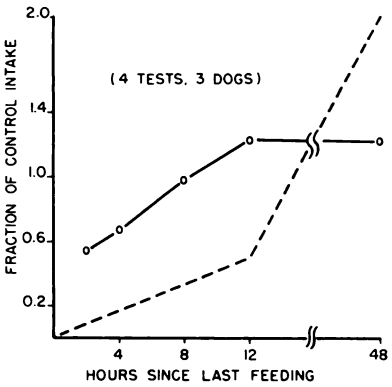


FIG. 9. Effect of interval since last feeding on amount of food eaten. Comparison is with control intake on a twenty-four hour schedule of feeding. Dotted line represents expected intake if amount eaten is directly proportional to length of abstinence from food. (Data from: SHARE, I. and GROSSMAN, M. I. Unpublished data.[10])

how much energy they have stored, is unknown.

## PRECISION OF REGULATION

Dogs maintained under standardized conditions of feeding show only small fluctuations in food intake and maintain their body weight with remarkable precision. For example, the data of Janowitz and Hollander[7] show that for three dogs during three ten-week control periods the mean coefficient of variation of food intake was 12 per cent and of body weight 1 per cent. However, small changes in feeding schedule can cause large changes in intake. Some previously unpublished observations made by Share and Grossman[10] illustrate this. Dogs, whose control intake had become stabilized when they were offered food once daily for forty-five minutes, were presented with food three times (for fifteen minutes each time) with fifteen minute intervals between offerings (Fig. 8). The intake during the first fifteen minute offering was equal to the control intake, but food was consumed at each of the two subsequent offerings so that the total intake was in considerable excess of the control intake. Under these circumstances it would appear that fully repleted dogs eat simply in response to being offered food.

Another demonstration of the same type of phenomenon is depicted in Figure 9. Dogs accustomed to being fed every twenty-four hours were fed at longer or shorter intervals. At two hours after the last offering, intake was 55 per cent of control; at three hours, it was 67 per cent; at eight hours, it was 98 per cent; at twelve hours, it was 103 per cent; and at forty-eight hours, it was 101 per cent. It is reasonable to assume that the magnitude of the energy deficit is approximately a simple linear function of time since the last feeding. It is then clear that under these conditions of sudden alteration of feeding schedules food intake is not accurately adjusted to size of deficit. Since these inaccuracies of regulation can be induced even when all feeding is by the normal route, it is not surprising that fractionation of feeding events may fail to produce predicted alterations in intake. It is for this reason that negative experiments cannot rule out hypothetical mechanisms.

It appears that the assumption that regulation is precise, that intake closely approximates deficit, may be invalid for many experimental situations. It follows that deductions based on this assumption may be misleading.

## COMMENTS

A number of factors which might be expected to serve as signals for cessation of eating have been considered. I have dealt mainly with those aspects of the problem which my colleagues and I have studied. Additional factors, such as osmotic effects, temperature effects, and others, which may be of as great importance as those studied, have been neglected. This serves to emphasize that the regulation of food intake is a multi-factorial process.

The best working hypothesis available is that these factors operate through the areas of the brain, especially the hypothalamic portions, which are concerned with facilitation and inhibition of feeding reflexes. This aspect of the problem has not been considered because in no instance is it known how a given factor sends its signals to the brain.

## SUMMARY

Many factors are concerned in the production of satiety or cessation of eating. Among these are a stomach distended either by food or

non-nutritious substances and, over a relatively long period of time, energy balance. On the other hand, food that has left the stomach, secretion of enterogastrone, or large amounts of intravenous glucose appear to have no effects on satiety. Although it has been postulated that the inhibition of feeding reflexes are carried through the hypothalamic portion of the brain, neither the precise pathways that mediate satiety nor the interrelation of the many factors causing cessation of eating are known.

## REFERENCES


1. Janowitz, H. D. and Grossman, M. I. Some factors affecting the food intake of normal dogs and of dogs with esophagostomy and gastric fistula. *Am. J. Physiol.*, 159: 143, 1949.
2. Share, I., Martyniuk, E. and Grossman, M. I. Effect of prolonged intragastric feeding on oral food intake in dogs. *Am. J. Physiol.*, 169: 229, 1952.
3. Janowitz, H. D. and Grossman, M. I. Effect of prefeeding, alcohol and bitters on food intake in dogs. *Am. J. Physiol.*, 164: 182, 1951.
4. Quigley, J. P., Zettelman, H. J. and Ivy, A. C. Analysis of the factors involved in gastric inhibition by fats. *Am. J. Physiol.*, 108: 643, 1934.
5. Janowitz, H. D., Hanson, M. E. and Grossman, M. I. Effect of intravenously administered glucose on food intake in the dog. *Am. J. Physiol.*, 156: 87, 1949.
6. Bernstein, L. M. and Grossman, M. I. An experimental test of the glucostatic theory of regulation of food intake. *J. Clin. Invest.*, 35: 627, 1956.
7. Janowitz, H. D. and Hollander, F. The time factor in the adjustment of food intake to varied caloric requirement in the dog: a study of the precision of appetite regulation. *Ann. New York Acad. Sc.*, 63: 56, 1955.
8. Lyon, J. B., Jr., Dowling, M. T. and Fenton, P. F. Studies on obesity. II. Food intake and oxygen consumption. *J. Nutrition*, 51: 65, 1953.
9. Janowitz, H. D. and Grossman, M. I. Effect of variations in nutritive density on intake of food in dogs and rats. *Am. J. Physiol.*, 158: 184, 1949.
10. Share, I. and Grossman, M. I. Unpublished data.


## DISCUSSION

Dr. John Brobeck (*Philadelphia, Pennsylvania*): These two possibilities you have given us are not mutually exclusive. You said feeding is not regulated precisely because it does not follow energy deficit It is possible that feeding does not follow energy deficit, but it is regulated on some other variable.

Dr. Grossman: I think the fact is that in spite of many types of variation in schedule, activity and so on, regulation is achieved, but the lags are so great that tremendous imprecisions can occur while the equilibration is occurring.

Dr. Brobeck: Regulation is not necessarily directed toward replenishing deficit of energy. Sometimes energy is replenished and sometimes it is not, depending on other circumstances.

Dr. Grossman: I think that statement is also correct. When re-equilibration has taken place, it does not necessarily mean that you have simply repaired deficits.

Dr. Eliot Stellar (*Philadelphia, Pennsylvania*): One may encounter failures of regulation in experiments of this sort due to a number of factors that might be operating. One of them is the factor of habit, which may have entered into the experiments of Dr. Grossman.

In experiments in the related field of specific hungers, a failure to make beneficial selections may occur because of previous habits of ingestion which have led to selection on, say, a taste basis. For example in the experiments of Dr. Harris with vitamin $B_1$ selection, the animals erroneously followed the flavor of anise, which had been associated with the vitamin $B_1$. On subsequent measurements when the anise was associated with a vitamin $B_1$ deficient diet the animals switched and ate the deficient diet, although they had continued to be deficient. There are other experiments which suggest the general principle that taste, habit factors, and other, including emotional inhibition or emotional interference, may enter into experiments on regulation over a period of time, to result in an imprecise measurement or an imprecise result.

Dr. Henry D. Janowitz (*New York, New York*): While the discussion has emphasized the imprecision of these regulations, I think we should not lose sight of the fact that when equilibrium was established, even by such circuitous routes as intragastric feeding, the precision of regulation was precise at the time of equilibrium. Thus, energy deficits were closely corrected by appropriate food intake, granting the initial inertia of the system. Deficits of 50 per cent were corrected, although it took several weeks for this equilibrium to be established, in the absence of pharyngeal and gastric cues.

Dr. Brobeck: There is no one necessary fat content for the carcass of an animal. When one speaks of replenishment of an energy deficit, it implies that the animal is going to eat until it obtains a certain concentration of fat. This is not true. One can change the concentration of fat simply by changing the composition of the diet, the environmental temperature, the availability of water, or the endocrine status of the animal. There are many different changes that will alter the concentration of fat.

DR. JAY TEPPERMAN (*Syracuse, New York*): Some years ago Dr. Stevenson did some experiments in which the responsivity of the regulatory mechanisms was made erratic by shifting suddenly from a high carbohydrate diet to a high fat diet, or vice versa. The suggestion was implicit in this that the regulatory mechanisms had become adapted, or accustomed, to regulating with a good deal of precision on one regimen and then when the regimen was drastically altered, the regulatory mechanisms were no longer adequate to the new situation.

Dr. J. A. F. STEVENSON (*London, Ontario, Canada*): I think that the experiments to which Dr. Tepperman is referring may be those that we did with Lundæk.

While there was some evidence of what you say, this was complicated by what appeared to be another factor. On changing, for instance, from a high-fat to a high-carbohydrate diet, we had the impression that the difficulty in adjusting may have been partly gastrointestinal in that the digestion and absorption processes had themselves become unadapted to carbohydrate. This was borne out by studies on the isolated diaphragms of such animals in that the diaphragms of the animals fed the high-fat or non-carbohydrate diet would not take up nearly as much glucose as those from the high-carbohydrate animals. We thought that the same thing might be occurring in the gastrointestinal tract.

I think that while there was an apparent upset of regulation, these experiments also showed this other factor, namely, an effect on the local tissues involved in the handling of food by the body.