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PHYSIOLOGY OF THE CONTROL OF FOOD INTAKE

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CONTENTS

INTRODUCTION AND SCOPE

Purpose and Extent

First we introduce the novice to the field by briefly describing the major phenomena and theories, with reference to other reviews for further discussion. This part of the review will also remind specialists of the diversity of behavioral, physiological, and ecological functions served by ingestion. Next we review in depth the many experiments that bear on the origin and function of neural or humoral signals arising from the acts and consequences of ingestion. The roles of these signals have been evaluated mainly by administering nutrients, neurotransmitters, or inert substances and observing their effects on food intake or food-motivated behavior—e.g. for rats, running in an alley or pressing a lever to obtain food. Finally we point

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out that our present knowledge does not allow definitive tests of current hypotheses, in large part because the conduct of experiments and presentation of data are not uniform. The diversity of data presentation forms makes it difficult and sometimes impossible to compare results of similar manipulations from different laboratories or even to compare results of the same investigator over several years. We suggest certain basic criteria that would ease the burden for reviewers in the future.

Methods of Study and Types of Control

Food intake is commonly measured by providing an animal or human subject with a mixed diet and measuring the amount consumed in fixed units of time, usually minutes, hours or days. However, in order to understand the physiological controls that lead to cumulative intakes at these time periods, it is necessary to divide the controls into phasic elements (those that initiate or terminate feeding or food-motivated behavior) and tonic elements (those that sustain a state of eating or a state of suppression of eating).

As a result of the operation of tonic and phasic controls (or perhaps it would be more accurate to state that these controls are inferred from the fact that) feeding behavior is episodic in most animals. All animals spend some portion of their time in quiescence (sleep for some), so that even grazing animals like cattle do not eat constantly (169). We shall refer to the times when feeding is the predominant activity of the animal as *meals,* and to those times when feeding is not occurring as *intermeal intervals.* While it may not be logically necessary to have both tonic and phasic elements controlling eating in order for meal patterns to occur, the limited evidence suggests that the controls operate as though such elements existed. The main evidence for this argument is differential effectiveness of physiological and neurological manipulations on the sizes of meals and intermeal intervals (15, 140, 165, 220, 259, 295).

Some types of control apparently act for only brief periods (hours) and are referred to as short-term, while others act for much longer periods (days or months) and are referred to as long-term controls. Signals for short-term controls include the osmolarity of gut contents, fullness of the gut, and fluctuations of hormone or nutrient levels in the blood. Signals for long-term controls could include body fat content (295) or cerebroventricular insulin level (213). Little is known about how these factors influence the tonic and phasic elements although some progress has been made (151).

Direction of Theories

Food intake is largely self-controlled. The absence of food promotes search and ingestion, while ingestion is self-limiting. Theories about food intake have concentrated on specifying sites where nutrients act to modulate inges-

tion. In addition, theories of food intake control have sought to determine what properties of nutrients are responsible for modulation of the sites.

Theories have also developed along neurobehavioral lines and have utilized psychological constructs to account for the variety of situations in which eating occurs. The concepts of hunger, satiety, palatability, and malaise, to name a few, have been commonly used to relate feeding behavior to a variety of circumstances that presumably end in a final common path in the nervous system. Although it is possible to review the controls of food intake without regard to these constructs, their pervasiveness in the thought of experimenters and use in the literature make them difficult to ignore. However, caution must be urged in attributing a final common behavior like eating to a unitary controlling center in the brain. It is now well-established that a variety of procedures induce eating by diverse neural pathways. This statement is based mainly on the differential effectiveness of brain manipulations on eating in response to food deprivation, body cooling, glucoprivation (reduction in availability of glucose for metabolism) and stress (8, 23, 80, 170, 186).

DEFINITIONS AND CRITERIA FOR THEIR APPLICATION

We here define such common words as hunger, appetite, and satiety in technical terms. Most investigators would agree with these definitions unless stated otherwise.

Hunger

Hunger refers to the internal state or level that disposes an animal or person to eat. It is manifest in verbal reports of desire to eat in man and inferred from human and animal behavior that increases in intensity when followed by the opportunity to obtain food and eat. Hunger is more than the sensation of an empty stomach as proposed by Cannon & Washburn (49), although stomach emptiness can be part of the mechanism by which hunger is induced. Furthermore, hunger is not a simple all-or-none state but may be graded in magnitude; it therefore has motivational properties that can be measured by amount and rate (135) of consumption (75) or rate of performance of an arbitrary behavior to obtain food (180, 255, 282).

Appetite

Appetite (246) refers to the state of willingness to accept food primarily for its pleasurable or rewarding properties. While reward undoubtedly plays a role in behavior driven by hunger, in appetite the urgency or need to replace nutrient is believed to be absent. Hunger is a necessity while appetite is a luxury. When food is eaten with no obvious internal need to be satisfied,

appetite is inferred as the intervening variable. The distinction between appetite and hunger therefore rests on determining the neediness of the subject, which is practically impossible to measure. Much attention has been devoted to what may be an artificial distinction.

It may be unnecessary to retain concepts (like appetite and hunger) whose study is unlikely to yield new mechanisms of operation for the control of food intake. Rather, it should be recognized that reinforcement (pleasure) and some degree of deficit always contribute to ingestive behavior. The components of "need" should be expanded to include psychological deficits from constant feeding with the same food and internal depletion at specific loci (221) rather than in the animal as a whole. Only an animal whose gastrointestinal tract is full and which has been fed on a variety of foods can be considered completely without deficits with regard to controls of food intake. When such animals can be induced to eat, we can infer the existence of appetite. It should be noted that not all authors distinguish appetite from hunger, and it has been suggested that the original definition, "desire to satisfy natural needs of the body," is still the most appropriate definition of appetite (25).

Food Intake

Food intake refers to the amount of nourishing substance consumed by a subject. Usually it is stated in terms of weight, calories, or volume of a mixed quantity of macro- and micro-nutrients, although intakes of separate sources of macro-nutrients such as fat, carbohydrate, and protein have been studied as well (201).

Satiety

Satiety (258, 296) refers to an internal state that leads to termination of eating. It is manifest by verbal reports of comfort, pleasantness, and satisfaction in humans, and by rest (9) in animals. It is also characterized by willingness to repeat the behavior that produced the state when it wears off. Like hunger, satiety is graded in intensity; its continuously changing value (280), in conjunction with other variables during a meal, leads to meal termination. That satiety is only one determinant of meal termination is shown by experiments in which rats are fed on quinine (bitter-tasting) food. Feeding stops but rest, which characterizes normal satiety, does not follow (9). We have found that human volunteers stop eating sooner, eat less, and give lower satiety ratings when they are fed a diet they like less than a control diet (24). If satiety were the sole determinant of the termination of eating, we would have obtained the same satiety rating even though less was eaten. Furthermore, subjects reported they would be unlikely to eat the diet again in another setting, therefore not meeting our criterion that satiety be an experience an organism seeks to repeat.

Malaise

Malaise is a state of discomfort manifested by verbal report in man and avoidance of stimuli associated with it in animals. An active debate currently flourishes in the literature over whether certain experimental treatments decrease food intake by inducing satiety or malaise (71, 93). Resolution of the issue by use of conditioned taste aversion was proposed by Deutsch (70, 71). According to this hypothesis, if illness is produced by an experimental procedure and a flavor is paired with that procedure, the animal will develop an aversion for the flavor and consume less of a food in which the flavor is placed. Smith & Gibbs (258), however, pointed out that conditioned taste aversions can be formed by association of flavors with intravenous injection of isotonic saline. They therefore questioned the assertion that illness is indicated whenever a taste aversion is formed.

Booth (27) has also pointed out that association of flavors with foods that produce earlier satiety or lower intakes, such as concentrated starch compared with dilute starch, will also produce conditioned reduction of intake for flavors paired with their ingestion. This reduction, however, occurs late in the meal, and is called conditioned satiety. It differs from conditioned aversion, which reduces intake from the very outset of the meal. Early and late are arbitrary designations. Booth (27) also based his conclusions in part on slowing of the rate of intake, which parallels the overall reduction. However, he used curves averaged from individual animals that stop at different times. Kissileff et al (136) have proposed that the question could be resolved more accurately by fitting equations to the cumulative intake curves to determine whether the rate of consumption at the beginning of the meal or rate of deceleration is affected by various conditioning procedures. To make matters even more complicated, it is not clear whether satiety and malaise are separable states, or degrees on a continuum of inhibition, or whether incipient malaise is a component of satiety in accord with the dictionary definition of being filled beyond need (37, 258, 296).

PHENOMENA TO BE EXPLAINED

Consistency of Food Intake

Theories of food intake control must explain the relative consistency in daily or weekly food intake of animals maintained on a diet of homogeneous composition under constant ambient temperature. Such consistency has been reported in most species of homeotherms—e.g. dogs (59), rabbits (89), rats (3), monkeys (105), quail (294), pigeons (314), and pigs (87). Adolph (3), for example, reported that food intake over 94 days in 7 rats averaged 5.5% of body weight per day with a coefficient of variation (standard deviation divided by mean times 100) of 10.7%. Hamilton (105) reported that a group of six monkeys had mean daily food intakes for a 4-week period

ranging from 88 g/day in the monkey whose overall average intake was lowest, to 347 g/day in the monkey whose overall average intake was highest. Within individual monkeys the coefficients of variation ranged from 19.9% to 28.5%. More noteworthy however was the stability in these measures over a year. The coefficient of variation for 13 4-week periods ranged from only 12.6 to 30.3. This consistency, which has been observed in other species as well, suggested that a control system for food intake corrects errors in daily energy balance to maintain a long-term constancy (172). This idea has been explored by the classic means of varying nutritive density of the diet and observing compensatory changes in food intake.

Response to Nutritent Dilution and Concentration

When the nutritive density of a diet is decreased by adding nonnutritive substances, food intake (measured in units of weight or volume) increases; when fat is added, thereby increasing nutritive density, food intake decreases (159, 277). However, the accuracy of adjustment in calories (i.e. compensation) is perfect only when the change in caloric density is small or when water is used as the diluent (see Table 1); the accuracy is not uniform across species. The literature on response to dietary dilution is large [see (107) and (108) for summaries]. We describe below the results from reports whose data are readily comparable in order to extract the most general statements, which in any case are limited by at least the following seven factors: (*a*) type of diluent, (*b*) duration of maintenance on the diet, (*c*) level of dilution, (*d*) fat content of the diluted diet, (*e*) time allowed for eating the diet, (*f*) body composition of the animal, and (*g*) species.

First, response to dilution is better when water is used as the diluent than when solids are used. Compare the results of Snowdon (266) with those of Kanarek (122) on Table 1 for rats, and the results of Porikos et al (212) with those of Campbell et al (48) for man. Because the Campbell et al (48) study was longer than that of Porikos et al (212), the second factor, time on the diluted diet, should be considered. The longer a subject is on the diet, the more likely it is that compensation will be completed [(26, 265, 279); see also Table 1]. The same conclusion applies to man [see data of Spiegel (269) in Table 1] and to monkeys (107). The third factor contributing to response magnitude is the degree of dilution or concentration. Adolph (3) showed that, with liquids, intake was within 10% of normal intake when the diet was diluted to 8% solids in water. When solids were used as diluents, full caloric compensation occurred in response to dilutions up to 50% with kaolin but only to 25% with cellulose. Beyond these levels of dilution, compensation was incomplete.

Addition of nutritive fat is the fourth factor that influences response to caloric dilution. High-fat diets result in excessive caloric intake (50, 179,

Table 1 Effect of nutrient concentration on food intake

Type of food	Caloric density	Species	Intake/day		Meal size		Number of meals	Access time		Avg. wt. (kg)	Reference numbers
			g or ml[a]	kcal	g or ml	kcal		hr/day	days		
Powdered chow	3.6	rat	23.85	85.86	3.0	10.8	8.86	24	15	.371	122
Above + 25% cellulose	2.7	rat	26.42	71.33	3.0	8.1	6.70	24	10	.371	122
Chow + oil	4.5	rat	20.4	91.8	3.1	13.95	9.38	24	10	.371	122
Liquid	1.8	rat	41.2	74.16	3.01	5.4	14.55	24	2–4	.348	266
Liquid ½ strength	0.9	rat	89.6	80.64	5.06	4.5	18.16	24	2–4	.348	266
Liquid ¼ strength	0.45	rat	144.4	64.98	7.57	3.4	19.73	24	2–4	.348	266
Powdered chow	3.5	rat	14.3	50	i			2	7	.271	265
Above + cellulose	2.1	rat	12.5	26.2				2	7	.234	265
Chow + fat	6.0	rat	12.9	77.9				2	7[b]		265
Chow + fat + cellulose	4.75	rat	16.1	76.3				2	7[b]		265
Chow + fat + kaolin	3.5	rat	22.0	77.1				2	5[c]		265
Pellets	3.6	rat	22.7	79.4				24	3[d]		265
Pellets + cellulose	2.1	rat	34	71.4				24	3[d]		
Ensure	1.35	monkey	453	612.5				24	15–60	5.7–8.8	107
Ensure	1.0	monkey	583	583				24	60	5.7–8.8	107
Ensure	0.5	monkey	1126	563				24	15–60	5.7–8.8	107

Table 1 *(Continued)*

Type of food	Caloric density	Species	Intake/day		Meal size		Number of meals	Access time		Avg. wt. (kg)	Reference numbers
			g or ml[a]	kcal	g or ml	kcal		hr/day	days[d]		
Metracal	1.0	human (gp A)$_h$	1902	1902	5.86	5.86	3.3	24	4–7		269
Metracal	0.5	human (gp A)	2009	1004.5	1164	582	3.45	24	4–8		269
Metracal	1.0	human	2463	2463	1118	1118	2.2	24	7–9		269
Metracal	0.5	human (gp B)	4288	2144	3232	1616	2.6	24	12–14		269
Mixed		human		3400				24	3[e]	103	211, 212
Mixed + 25% dilution		human		2516				24	3[e]	104	211
Mixed + 25% dilution		human		2822				24	3[f]	104	211
Mixed		human		3600				24	6		211
Mixed + 25% dilution		human		3000				24	12		211
Liquid formula	1.0	human[g]	1795	1795				24	5–8	59	48
Liquid formula		human	2692	1777				24	5–7	59	48

[a] Units are grams for solids, ml for liquids.
[b] Second week on diet.
[c] Last 5 days on diet.
[d] Last 3 days of 1 week period.
[e] First 3 days on diluted diet.
[f] Second 3 days on diluted diet.
[g] Based on 3 subjects who received both 1.0 and .66 kcal/ml concentrations.
[h] Group A and group B were treated differently in the experiment. A received meals both inside and out of the laboratory, while S's in B had to come to laboratory to eat all meals.

277), but compensation for their dilution is better than it is with low-fat diets (265). The fifth factor is time of access, in hours per day, to food. When access is limited, the response to dilution is blunted and/or requires more days to reach equilibrium (26, 265). The sixth factor is body fat stores. Obese animals respond more poorly to dilution than lean ones (42, 127, 279), although this effect can be minimized by using liquid diets (60, 284). These results are consistent with observations that some obese rats are hyperreactive to the sensory qualities of the diet (60, 127, 281). When a pelleted rather than a powdered diet was diluted with 25 or 50% kaolin, obese rats with ventromedial hypothalamic lesions increased their food intakes as much as did control rats (265a).

Finally, the factor of species difference in response to dilution must be considered. In order to make a comparison among species, all other factors should be held constant. Since most studies have not utilized the comparative approach, an accurate assessment cannot be made. However, based on the closest approximations, it appears that dogs, cats, and guinea pigs respond poorly to dilution, while rats, monkeys, and humans respond better. For further information, consult the references listed by species in Table 2.

Response to Changes in Energy Expenditure

Although relative long-term consistency in food intake is circumstantial evidence for existence of a regulation, it is not conclusive. Dilution experiments suggested that within limits nutrient intake is preserved. Evidence that the energy in the food is the quality controlled was provided by experiments that showed compensation in food intake when energy expenditure was varied. These experiments thus shifted emphasis to regulation of the energy balance of the body rather than of nutrient intake (42a, 172). Energy expenditure can be varied by changing the activity level of the animal by

Table 2 Studies using dietary dilution

Species	References
Rat	3, 50, 265, 265a, 266
Dog	59
Cat	121
Guinea pig	110
Hamster	253
Gerbil	126
Quail	294
Ruminants	183
Human	48, 211, 212, 269, 309

enforced exercise or restraint, as well as by changing the environmental temperature.

Hamilton (103) has reviewed experiments on the effects of ambient temperature changes on food intake. Since that review appeared, investigators have concentrated on the pattern of eating by which changes in food intake are mediated. Food intake is inversely proportional to ambient temperature, and the major effect of temperature is on the frequency of meals (132, 138, 139, 295). However, the time course of adaptation to a given ambient temperature suggests that energy requirements are not the only determinant of food intake of a mixed diet. Within a few days after a change in ambient temperature the food intake of rats returns toward normal (102, 295).

An early demonstration of the effect of exercise on food intake is that of Mayer et al (173). They showed a slight decrease in intake as energy expenditure increased from sedentary levels and then a linear increase, proportional to the time the female rats spent on a treadmill, up to 5 hr per day. Beyond 5 hr per day of exercise, food intake decreased. Nikoletseas (193) has recently pointed out that the generality of this effect can be obscured by other factors: sex of the animal, time allowed for feeding, spacing of exercise bouts, and duration of the experiment. The following examples illustrate these limitations to the generality. Food intake of female, but not male, rats increased with exercise (199), although intake of male rats increased if a variety of foods was available (7). Food intake was depressed immediately after exercise, even up to 24 hr, but overshot after a day without exercise both in men (76) and rats (274). Regularly spaced bouts of exercise decreased food intake less than irregularly spaced bouts, and after adaptation the decrease was reduced (274). Limiting the time allowed for eating after exercise resulted in failure to increase food intake, and the imbalance in expenditure led to mortality (233), which could be offset by prior adaptation to the feeding schedule (232). The decrease in food intake following exercise was also not observed in 23-hr fasted male rats that had been trained to run prior to introduction of the deprivation schedule (192). Increases in food intake were seen during weeks when energy expenditure was increased in lean (207) but not obese (304) women.

Effects of Changes in Body Nutrient Content

Excesses or deficiencies in body weight, which reflect body nutrient content when transient changes in body water are controlled, lead to changes in food intake in almost all studies of this phenomenon. Adolph (3) did not observe increased food intake upon restoration of food supply to young rats (150–300 g males) deprived of food (but not of water) for either 1 or 6 days; he did observe such increases upon restoration when both food and water had been removed. However, in older rats weighing 350 g or more, deprivation

of food for 24 or 48 hr increased food intake from about 22 to about 28 g on the first day of restoration (11, 104, 157, 158, 159, 209). This increase gradually declined over 3–4 days to the pre-deprivation level. Deprivation for longer than 48 hr decreased the initial day's intake to 26 g in 3-day-fasted, 24 g in 4-day-fasted, and 20 g in 6-day-fasted rats (104). However, following fasts of greater than 2 days, food intake gradually increased after the first day of restoration and remained elevated for a number of days proportional to the length of the fast. However, in no case did the total excess intake exceed the amount taken in a single 24-hr period prior to deprivation (160).

Increases in food intake also occurred when body energy was depleted by limiting caloric intake, either by means of providing less food (209), adding quinine to the food (158), or reducing availability of water (158). Slightly larger food intakes were seen intially upon restoration of ad libitum food following partial restriction of food (209) or following feeding of a nonnutritive diet of vaseline and cellulose (104), than following complete food deprivation, even when animals were reduced to the same body weights. It has been suggested that either gastrointestinal factors (104) or starvation diabetes (209) accounts for the reduced intake of the completely starved, in comparison with the food restricted rats. However, body weight is not a perfect index of body fat mass. We suggest that hypometabolism (61) in the completely starved animals may preserve more fat in them than in the restricted rats, and that the metabolic contribution of this hypothetically larger fat mass may reduce hyperphagia. Hypometabolism could also be responsible for the fact that starved rats recovered to the same body composition as unstarved rats with an increased food efficiency (22) [ratio of weight gain to food intake].

Not all species respond as the rat does to deprivation, and not all studies on the rat find uniform effects, particularly when only limited periods were available for eating [see (14, 158) for further discussion of the rat]. Dogs (2, p. 324) and monkeys (176) made up deficits well even in a limited time. Rabbits made up deficits partially by increasing food intake, (164) as did guinea pigs (110). Hamsters did not make up deficits by increased food intake unless on a high fat diet (39) consisting of sunflower seeds; otherwise they lost weight that was not completely recovered (253).

Weight gain induces reduction of food intake. The magnitude of this reduction depends on several factors: the means by which weight gain was induced, amount of weight gain, age of the animal, and diet. Food intake was reduced after the following weight-gain-inducing procedures were terminated: (*a*) forced intubation of excess food (52, 230) and (*b*) overeating induced by either electrical stimulation of the brain (272) or injection of long-acting insulin (114). Food intake declines only gradually during weight

gain induced by adding fat to the diet (81) or offering concentrated sugar solutions (124). The precise effect on food intake of terminating these procedures has not been studied. However, a precipitous drop would be predicted, because switching rats from highly palatable "snack food" diets to chow after they have gained weight results in food intake reduction (88, 230, 250), although this effect is not uniformly seen (227). It is not clear whether strain differences are responsible for these different results; but this possibility is likely because rat strains are differentially susceptible to the fattening effects of high-fat diets (244) and varied cafeteria diets (231), possibly as a result of the ability of brown fat to burn off the excess intake (231).

It has been reported (see 151) that after weight-gain inducing procedures are terminated rats are hypophagic until they return to their initial body weight, but the actual functional relationship between food intake and body weight has not been precisely specified. Such a relationship is important to know, because it would suggest the type of mechanism (e.g. constant input vs trigger at a certain level) by which body weight could influence food intake. Furthermore, it is important to separate the effects of the various treatments that induce weight gain from the weight gain itself in order to determine what factors are responsible for the apparent effects of changes in body nutrient stores. Obviously, much more work is needed in this important area of investigation.

Microstructure of Eating: Periodicity and Rate

Another basic phenomenon requiring explanation by theories of food intake control is the intermittent occurrence of feeding and its change in rate throughout the meal. Richter (217) was the first to record feeding patterns in the rat. He found meals regularly spaced at about 4-hr intervals. Subsequent investigators have found that the temporal pattern, like total daily food intake, varies quantitatively with a variety of conditions [see (295) for details].

One of the most interesting meal pattern phenomena is the Le Magnen [(267), p. 74] postprandial correlation, a high and significant correlation between the size of a meal and the interval that follows it. Le Magnen and colleagues (152, 155, 156) also noted absence of correlation between the size of a meal and the interval that precedes it during spontaneous feeding in nondeprived rats. This finding was surprising because previous studies had suggested that the interval of deprivation increases the size of subsequent meals (14). Apparently different rules apply to nondeprived animals. This finding has been found in most species [see (151) for details], including man (20). The Le Magnen correlation refocused attention from a search for an increase in depletion factors that control feeding to a search for satiety factors whose decrease releases feeding from inhibition (30).

Many factors influence the meal pattern. These include species, sex, nutritional status, and type and nutrient density of food, as well as phase of the light-dark cycle and effort required to obtain food. The complex effects of these various factors have been reviewed (55, 295). An excellent discussion of the role of metabolic depletion and repletion in relation to meal patterns has recently been completed (151). In the rat, meals vary in size from 3–10 kcal depending on the density and palatability of the diet, and intermeal intervals range from 20 min to 6 hr depending on meal size and effort expended to obtain food. Intake during the dark phase of a 12–12 light-dark cycle is generally twice as large as during the light. Finally, rats tend to be hyperphagic (eating more than the energy they expend) in the dark and hypophagic (eating less than the energy they expend) in the light (154).

Rate is another microstructural characteristic of eating that has received attention, recently. Most observers agree that the rate of eating gradually drops during a meal (120, 254), although this phenomenon is more apparent in deprived than nondeprived subjects (see Figure 1). Mathematical models (64) and equations (136, 174) have been proposed to describe and explain the shape of curves of cumulative intake during a meal under a variety of conditions. Deprivation and palatability increase the initial rate of eating, while gastrointestinal overfilling induced by ingestion of hyperosmotic fluids slows the rate of eating more quickly during the course of a meal (64, 135). An important clinical issue, still controversial, is the idea that rapid eating results in greater intake. This hypothesis is suggested by Jordan & Spiegel (119), who found increased intake when they increased the rate of delivery of food via a pump or simultaneously delivered diet into the stomach while subjects were taking food from the pump by mouth. It is disputed by the mathematical model of Booth & Mather (38), which suggests that an increased rate of eating will activate post-absorptive satiety systems faster than normal and will therefore hasten satiety. The influence of body weight on rate of eating has also been studied. Some studies report higher rates of eating in obese people, whereas others report no differences [see (270) for review], although most of these studies are confounded by interactions with the type of food and sex of the subject (136). In rats the rate of eating declines after deprivation-induced weight loss (158). The rate of eating after overfeeding has not been reported, although after obesity induced by ventromedial hypothalamic lesion it was found unchanged (284).

Nutrient Selection

Another important basic phenomenon in the control of food intake is the ability of animals to select the proper balance of the three major macronutrients, protein, fat, and carbohydrates, from an array of foods with mixed macronutrient content or from a selection of relatively pure macronutrients themselves (78, 201, 218, 235). The amounts of the three macronutrients

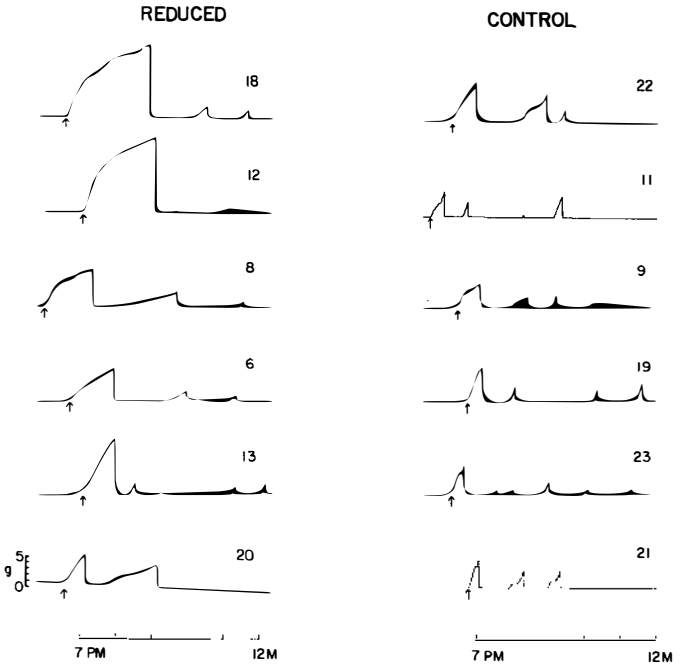

Figure 1 Meal pattern profiles of rats following either a period of 20% weight reduction (left side) as a result of being fed five small (1.5 g) meals per day every 2 hr during the light phase, or no restricted feeding (right side). Both groups were fasted the night before these records were taken and given the same 5 small meals. The last meal was 2 hr before these records were collected. Food was 45 mg Noyes pellets taken from a pellet detecting eatometer (132a). The meal pattern profiles were generated by computer analysis adapted for solid food intake, collected by printout counters (15). (H. R. Kissileff, A. Schmader, unpublished data, 1976).

selected vary with the condition of the animal [e.g. exercised vs sedentary (7, 56), diabetic vs normal (84, 219)], the selections available (78), and the experimental treatments [e.g. insulin administration (125) or ventromedial hypothalamic lesions (123, 131)]. However, under nonintervention conditions, the ratios among spontaneous macronutrient intakes tend to be remarkably constant in humans (percentages of total calories were 11–15% from proteins, 50–58% from carbohydrate, and 26–37% from fat), and somewhat more variable in the rat (see Table 3). Successful survival on self-selection diets also depends on acceptable orosensory qualities of the diet, and Epstein has wisely stated: "The wisdom of the body is not an infallible guide to nutrition" [(78), p. 201].

Availability and Palatability

Availability refers to the ease with which the animal obtains food [procurement cost (53)] and palatability refers to the orosensory qualities that determine acceptance (134). The latter definition may not be accepted by

Table 3 Percentages of macronutrients chosen on self selection diets

Species	Daily intake (kcal)	Percentage of energy intake			Age[a]	Weight[b]	Sex[c]	Source
		Fat	Protein	Carbohydrate				
Rat	46.3	64.0	16.0	20.0	59	130	F	218
Rat[g]	130.0	34.4	9.0	56.6	—	387	M	248
Rat	62.4	26.4	27.5	46.1	49	128–172	F[d]	123
Rat	86.5	18.0	35.0	47.0	—	202–271	F	125
Human	3432.0	33.3	11.8	53.3	19	70	M	76
Human	3296.0	26.1	15.3	58.6	44	103	M & F	212
Human	2460.0[e]	35.0	11.0	54.0	16	55	F	207
Human	2900.0[f]	37.0	13.0	50.0	16	55	F	207
Human	2233.0[e]	31.6	15.8	52.6	42	92	F	303a
Human	2345.0[f]	32.7	15.8	51.5	42	92	F	303a

[a] Years for man, days for rat
[b] g for rat, kg for man
[c] M = male, F = female
[d] Sham group, preoperative
[e] Nonexercising
[f] Exercising
[g] Experiment 2, con-sham

all, as some authors (149, 312) consider the palatability to be a joint function of the animal and the food. However, we believe that in order to delineate the controls of food intake, it makes more sense to consider palatability a quality of the diet and to attribute changes within the animal to changes in its response to the same diet under different experimental conditions (e.g. after fasting, overfeeding, or conditioning).

When food becomes more scarce or more costly to obtain, intake gradually declines (122). When the palatability of the food changes, intake changes with it (224); foods whose acceptance or preferability in short-term tests is high will be overconsumed (281), and foods not preferred in short-term tests will be underconsumed. These changes in intake are not constant over time, however. Rats compensate for changes in diet palatability over time and can maintain almost normal growth on diets that were initially almost totally unacceptable (144, 208). Because units of palatability and availability (or effort) have not been scaled in a standarized way, intake as a function of palatability or effort has not been precisely described. On the theoretical plane, at least two possible relations could be seen. Palatability could yield a graded response in intake if its effects summed with other controls, or it could yield a dichotomous (either high or low) response in food intake if it simply served as a trigger to prevent or prolong eating.

Food variety is also an important factor in intake control. When people were fed three courses, each of a different-flavored yogurt, they consumed more than when the same flavor was given at each course (226). The variety effect has also been observed in rats (150).

Patterns of intake as well as total intake are affected by both palatability

and availability of food. As the diet becomes less palatable, meals become smaller and more frequent (249), but they become larger and less frequent as the effort to obtain them is increased (122). For example, on a sweetened condensed milk diet rats took 18 meals per day of 3 ml. When the diet was adulterated with quinine, meal size dropped to 1.7 ml and meal frequency rose to 20 meals per day (249). Meal frequency dropped from 8.8 per day with no effort to .62 per day when 640 lever presses were required to obtain access to the food. Meal size increased from 3 g per meal to 12 g per meal under these conditions. The average rate of eating was unaffected by the increased effort (122).

Summary of Phenomena

When experimenters manipulate the composition of the diet and the time of access to it or when the nutrient content of the animal is altered experimentally, compensatory responses are made in such a way as to restore the prior state of intake of the animal or its body composition. Such responses suggest the existence of detectors that monitor either the intake or its consequent effects on body composition or distribution of nutrients within the body. They also suggest that some response system exists that brings about appropriate changes in intake or energy expenditure. However, responses to some changes in diet composition, such as to those that affect primarily sensory rather than nutritional quality, contradict the idea that intake is determined solely by compensatory changes in response to perturbations in body constituents (283). Not all phenomena can be explained by any simple account of the control of food intake, such as the contraction of an empty stomach (49) or depletion or reduction in utilization of a critical metabolite (172) or even metabolites in general (86, 128).

THEORIES

The theories advanced to explain the results described above are either homeostatic (i.e. they posit attempts to preserve constancy in a variable) or nonhomeostatic. The homeostatic hypotheses often suppose the existence of a reference value or set point (302, 303) against which current values in the regulated variable are compared. Such theories suggest that the discrepancy between this set point and the current value is then used to drive or inhibit a response such as eating. Since no direct evidence for set points has ever been found, it has also been proposed that the sensitivity of detectors and their connections to a response system could restore imbalances and therefore act as a regulatory system (45, 302). Several homeostatic theories of feeding have been advanced over the last 30 years. For those that have been repeatedly reviewed we provide only brief descriptions here and refer the

reader to other reviews (4, 40, 203) for details of evidence in their support.

Nonhomeostatic theories do not posit mechanisms that preserve constancies. Instead, such theories assert that the primary control of food intake originates in the configuration of the environment and the genetic adaptations built into the animal to cope with that environment, or to psychological constructs such as drives or incentives that induce the animal to engage in feeding behavior not for the purpose of restoring some deficiency but in order to obtain pleasure or reward. While a single unifying theory would be preferable to the present dichotomy, no such theory exists; the mathematical model of Booth & Mather (38) is an attempt to unify both types of theories in a rigorous way.

Homeostatic Theories

The homeostatic theories propose that a variable is regulated [i.e. maintained constant by means of detectors for its value or some function of it (44)] and that controls (management of rates of functioning) are set in motion to accomplish these regulations. Two kinds of homeostatic theories can be distinguished: those proposing that specific chemicals in the body are regulated [e.g. fats, carbohydrates (mainly glucose), or proteins (i.e. specific amino acids)], and those that propose regulation of energy or some function of it such as body temperature. The lipostatic theory, for example, proposed that depot fat was the regulated variable and that rates of food intake and energy expenditure were its controls (128, 295). The glucostatic theory proposed that utilization of glucose by privileged cells was maintained constant by initiating eating when utilization was low and inhibiting eating when utilization was high (79, 172). The aminostatic theory (178) likewise proposes that excesses and deficiencies of plasma amino acids are responsible for initiating or inhibiting food intake.

Another now-classical theory that attempted to link all these changes was the thermostatic theory (43, 45), which proposed that the heat generated by metabolic fuels either stimulated or inhibited feeding in accordance with the body's need to maintain a constant temperature. Recent adaptations of this theory propose that the energy produced by the metabolism of absorbed nutrients is monitored (28). However, neither the location of the detectors that perform this function nor the nature of the energy being monitored (i.e. electrical, chemical, or thermal) has been determined. The detectors could be in the brain, since it has been established that thermal detectors exist in the hypothalamus (106). There are, however, a number of difficulties with a strict thermal theory (see 86). Chemoreceptors have likewise been discovered in the brain (5, 198), but their relation to chemical energy remains a mystery. Evidence has been advanced for the liver as the organ that monitors the state of the body's energy stores. It has been proposed that "hunger

arises in the liver when fuel delivery from the intestines and adipose tissue is inadequate for the maintenance of body functions without significant hepatic contributions" [(86), p. 423].

The problem of the location of detectors and effectors for homeostatic response has been central to discussions of ingestive behavior for decades and merits more consideration than our brief review can provide. We (295) recently reviewed the status of the "dual center" theory originally proposed by Brobeck (42a). In brief this theory stated that feeding was elicited by a lateral hypothalamic center that was inhibited by a ventromedial hypothalamic center as a result of certain (unspecified) post-feeding changes in the body. When the food eaten was disposed of, the lateral hypothalamic center became active again, and the cycle was renewed. Although the concept of diffuse excitatory and inhibitory systems has replaced that of discrete centers (273), the notion of dual controls, one that excites and one that inhibits feeding, is still very much a part of most thinking about the neural control of intake. Evidence for the theory comes from the incontestable facts that (*a*) lesions (46) or anesthetization (77) of the ventromedial hypothalamus induce hyperphagia, while stimulation of it inhibits eating (143); and (*b*) lesions of the lateral hypothalamus induce aphagia (6) or hypophagia, while stimulation of it induces eating (181). The theory was also tied to chemostatic theories by locating detectors in the ventromedial hypothalamus (128, 172). This part of the theory initially ran into difficulty when anatomically direct stimulation by injection of putatively monitored metabolites failed to suppress food intake (77, 298) in acute experiments. However, it now appears that chronically administered nutrients do suppress food intake when injected intracranially in both the ventromedial hypothalamus (203, 205) and ventricles (66, 67, 306). Booth (30) seriously questions the interpretation of the lesion/stimulation approach, and his cautious critique should be read by any serious student of food intake.

The other suggested major site for homeostatic control of food intake is the liver. Russek (236) first proposed that hepatic glucoreceptors were involved in feeding because intraperitoneal glucose depressed intake more than equal doses injected into the jugular vein. According to current versions of the theory (237, 238), hunger is the result of decrease in the carbohydrate reserves signaled to the brain by discharges from the hepatocytes in the liver. The pathway for these discharges is in dispute (17, 162, 238). The system operates as follows: "Some metabolite of the glycolytic chain (i.e. pyruvate), related both to liver glycogen content and glucose input of the hepatocytes, has an hyperpolarizing effect on their membranes, perhaps through an increase in the sodium pump. Thus, hunger would normally appear when intestinal absorption and liver glycogen (and liver pyruvate) decrease to a certain critical level" [(237), pp. 137–38]. Note that

the wording is almost identical to that of Friedman & Stricker (86). Hyperpolarization and disappearance of the hunger discharges would occur as soon as absorption of glucose and/or amino acids from the intestine increased liver pyruvate, thereby inducing satiety. "Preabsorptive satiation is hypothesized to be caused by a reflex secretion of intrahepatic adrenaline from hepatic chromaffin cells located in the portal spaces [(171, 216)], elicited by information originating in the oropharyngeal, gastric and duodenal receptors [(63, 189, 190, 197, 252, 292)]. Duodenal (and possibly gastric) glucose and amino acid receptors might be the unconditional afferentation of this reflex, while oropharyngeal receptors and gastric distension receptors might produce a conditional effect which can be adapted to the changes in caloric content of food" [(237), p. 138]. Russek goes on to conclude that hepatic receptors might be the most important receptors determining hunger and satiety because "all the numerous factors that have been shown to influence food intake may act as modulators of this mechanism" [237), p. 141]. This is probably the most comprehensive theory proposed since the dual center theory and its chemostatic associates. It is heuristic, like the old glucostatic theory, because the major metabolic fluxes of the body converge on the liver. It is supported by the facts that intraportal injection of adrenaline and/or infusion of glucose inhibit feeding while equivalent doses elsewhere are less effective (36, 194, 196, 240). Electrophysiological studies support the existence of receptors (239). The theory has not gone unscathed, however; its critics point out that vagotomy fails to affect food intake patterns (162) and that glycogen levels gradually rise during the night and fall during the day (153), following, rather than leading, accumulation in food intake. Russek has responded to these and other criticisms (238), and the theory certainly merits further testing.

Two other organs, the stomach and intestine, have been considered as primary foci for homeostatic theories of food intake. McHugh & Moran (177) consider them as a unit, such that the intestine controls the rate of stomach emptying according to caloric homeostasis of emptying rate. Smith & Gibbs (258) and Deutsch (70) view them as units providing independent contributions. According to each of these authors, neural and/or humoral signals arise in these organs that inhibit food intake. When the signals are absent, intake will occur again. This theory is appealing because of its simplicity and because it makes easily tested predictions about the effects on food intake of manipulating the stomach and intestine by means of loading or emptying them, by stimulating or ablating their neural connections, or by simulating actions of their hormones. More of this evidence is detailed in the section on nutrient administration, below. Here we outline only the most compelling evidence and indicate the theory's limitations.

McHugh (175) has shown that caloric intake could be controlled by

distension of the stomach, which is in turn controlled by an intestinal mechanism that operates as though calories delivered to the intestine were the key signal controlling emptying of the stomach. Accordingly, preloads of the three macronutrients in equicaloric amounts suppressed subsequent food intake by the same amount (176) and emptied from the stomach at the same caloric rate (177). These results suggested the possibility that the "regulation of caloric delivery by the stomach could have a direct role in the control of food intake" [(177), p. R259]. The stomach and intestine could play a role in the phenomena of feeding we have described above only if emptying were controlled by some function of previously eaten food that had released its calories in a detectable way (i.e. by generating heat or being converted to detectable nutrient store). The theory predicts that stomach emptying will be slower and feeding inhibited after caloric intake exceeds energy expenditure. Doubts about such a mechanism, expressed by Van Itallie et al (295), now seem to be receiving confirmation in more recent studies by Moran & McHugh (185). Two predictions from the theory failed. First, glucose and xylose (a poorly metabolized pentose) leave the stomach at the same rate, yet only glucose contains potentially detectable calories. Nevertheless, each preload results in equal suppression of intake in a 4-hr test. The caloric deficit incurred after the xylose preload is made up the following day. Second, fructose leaves the stomach twice as rapidly as glucose, yet both hexoses inhibit food intake equally in a 4-hr test. Nevertheless, glucose inhibits food intake more than fructose during the first 80 min.

Thus although the gastrointestinal theory of homeostatic control of food intake cannot always account for the phenomena of regulation of energy balance, it can provide an explanation for satiety, whose putative link with energy expenditure must still be provided.

Nonhomeostatic Theories

Three major types of nonhomeostatic theory have been proposed: ecological, psychological, and computable. They differ from the homeostatic theory in that they do not posit the maintenance of a constancy in some body constituent. They do not deny the existence of regulation but propose that it is handled by physiological rather than behavioral processes. The ecological theories propose that feeding behavior is simply one of several alternative behaviors an animal can perform at any given time, and that the selection of a behavior is determined not so much by internal state of the animal as by ecological variables such as cost, abundance, and value (53). According to the theory, animals use an optimizing strategy for controlling meal patterns. An optimal feeding strategy maximizes energy intake relative to the time and/or energy spent feeding. This theory predicts that animals

will reduce meal frequency and increase meal size as the effort required to obtain food is increased, a prediction borne out in several species (54, 111, 121, 122). Obviously, the theory is a viable alternative to homeostatic theories for explaining meal patterns; but it certainly is not as general, since it does not attempt to explain the many other phenomena, such as nutrient selection or the variety of meal pattern responses to caloric density, deprivation, or palatability.

The second nonhomeostatic theory, reinforcement or incentive theory [see (288) for discussion], proposes that feeding, once initiated (by an unspecified mechanism), is maintained by certain sensory qualities of food that activate "reward" neurons. These neurons can only be activated by the food when the animal is hungry (228). These neurons are in turn modulated by the internal states of the animal, such as levels of hormones or metabolites. This proposal differs from homeostatic theories in positing no detection of departure from a set point to which the system must return after a disturbance is removed. Reinforcement theory suggests that food intake is controlled by cycles of depletion that permit reward neurons to be activated, and of repletion that block their activation. Behavioral evidence in support of this theory comes from studies showing that brain stimulation at certain sites both reinforces operant behavior (i.e. causes animals to sustain responses that result in further stimulation) and elicits feeding (113, 168). Furthermore, modulation of the reward effects of brain stimulation is obtained by body weight manipulations (112), and body weight manipulations also influence the ingestion of palatable solutions (47, 99, 184, 204).

The third type of nonhomeostatic theory is computable theory (i.e. food intake quantitatively predicted from physiological variables such as rates of stomach emptying, absorption, and metabolism), developed most fully by Booth and his colleagues (30, 33, 38). This theory accounts for meal patterns, adjustments to changes in energy balance, and rewarding effects of sensory quality in combination with energy flows, gastroduodenal control of absorption rate, and learning. It is predicated on the idea that feeding is initiated when net energy flow from lean body mass is detected and stops when there is a net energy flow to lean body mass, provided that orogastrointestinal cues are present, which have been associated with previous energy flows to lean body mass (31). The accuracy of computable theory exceeds that of nonmathematical theories and permits the inclusion of a greater number of variables. Since the components of the model can be manipulated mathematically, the theory permits accurate prediction of the effects of a particular treatment on all variables. The advantages and disadvantages of such a theory have been discussed (30, 38, 182). The theory has yet to incorporate the effects of neurotransmitters and hormones but is

presently the most comprehensive of all theories and has the potential to surpass all other theories in accuracy of prediction.

TESTS OF THE THEORIES BY NUTRIENT ADMINISTRATION

Dependent Variables

The predominant theory is that control of food intake is energostatic (see the section above on Homeostatic Theories). The major evidence for this theory is the reduction in feeding activity when nutrients are administered and the lack of effect of administering nonnutritive substances. These reductions have been measured in terms of consumatory (amount eaten) and appetitive (performance of arbitrary responses to obtain food) behaviors. The major dependent variables used to assess consumatory behavior are (*a*) total daily food intake, expressed in units of weight, volume, or energy or (*b*) intake at a single session lasting either for a fixed time (e.g. 1–12 hr) or until the subject stops eating for a fixed interval of time. Within each of these measures some finer-grain analyses have been attempted. Meal patterns have been analyzed to determine whether administration of nutrients affects an onset or termination (95, 215, 285) mechanism for control of daily intake, and rate of eating during the course of a meal has been analyzed in the single-meal situation (65, 136).

Appetitive behavior has also been used to assess the effects of nutrient administration when the amount of consumatory (133) activity is limited. Animals are trained to press a lever to obtain food; the rate of pressing on a low-density reinforcement schedule (i.e. several presses are required to obtain a single aliquot of 40–100 mg) is the measure of feeding activity (137, 262a). These details are emphasized at the outset because inconsistent results could be explained by differences in both dependent and independent variables.

Independent Variables

Various manipulations have been shown to influence the outcome of nutrient administration experiments, including type of substance, rate and frequency of administration, interval from administration to testing, nutritional status (hours of deprivation, prior feeding history, body weight), species and surgical preparation, route of administration, and test diet for determining the effect of the experimental treatment. With such an array of factors it is little wonder that it is difficult to make sweeping generalizations. Nevertheless, there is universal agreement that prior administration of nutrients reduces both appetitive and consumatory behavior. This generalization is in accord with predictions of the energostatic theory. On the

other hand, quantitative details differ across the range of independent variables.

Type of Substance

In this section we consider the effects of administering different substances when species, route, rate, and other variables are held constant; in subsequent sections we consider the effects of other variables when substance injected is held constant. We deal with interactions (i.e. effects of one independent variable that are not uniform in combination with other independent variables) along the way rather than in a separate discussion at the end. The effects of route of administration are discussed in the section on mechanisms, below, in relation to the issue of sites where nutrients and nutrient derived signals act to influence food intake.

This section addresses three questions: (*a*) How well does a subject (animal or person) compensate for administration of a nutritionally adequate mixture of nutrients to its body? We evaluate this response by means of an index known as the "suppression efficiency" (215), which is the amount of reduction in voluntary intake expressed as a percentage of the administered load. (*b*) How much of such reduction is attributable to bulk in the gastrointestinal tract? This question is answered by comparing the effects of administering nonnutritive, poorly absorbed, or poorly metabolized substances with those of administering nothing at all. (*c*) Do nutrients have specific chemical effects, or do they reduce food intake by some common property such as energy release (28), its time derivative, power (191), or osmolarity (65, 262, 264, 287)?

Loads of Nutritionally Adequate Mixtures

The hypothesis that food intake is controlled by a homeostatic mechanism predicts that disturbing the system by overloading the body with nutrients should be precisely compensated for by reduction in intake equal to the magnitude of the load. If this homeostatic hypothesis were substantiated, it would be logical to determine next what aspect of nutrient loads (including their bulk, which theoretically could be regulated) is detected. In two early tests of this hypothesis, deprived animals were offered food [a solid food for dogs (116) and milk for rats (18)] in two sessions separated by a short interval. Intake was almost the same as it was in the control condition, which was a single session (see Table 4). However, if the food was placed directly in the stomach first, intake in the second session was not reduced as much as it was by food actually eaten in the first session. This difference between second session intakes following eaten vs administered food was smaller in the rat feeding on chow (263), than on milk (compare lines 3 and 4 on Table 4). In monkeys (177a), compensation was

almost perfect (lines 8–10, Table 4). In human subjects (269), who were only 3–4 hr deprived, when oral intake in the first session was rapid there was a failure to compensate by adequately reducing intake in the second, so that two sessions of intake, one after the other, resulted in greater intake than a single session. Results of these types of studies depend on the choice of foods and cognitive state of the subject [see (270) for an exhaustive treatment of this paradigm]. Even though compensation was incomplete, reduction in intake was proportional to the size of the load, when loads of different amounts were given [(300); lines 5–7, Table 4].

Some of the trends in these acute studies suggest that better compensation might be seen with animals on ad libitum access to food and with liquid rather than solid foods. It was therefore surprising that Thomas & Mayer (285) did not find any better compensation obtained by use of chronic intragastric infusion of liquid diet than the earlier studies had found using acute injections (compare lines 11 & 12 with line 3 in Table 4). In another study (215) in which intragastric infusions were programmed to correspond to periods during which the animals normally ate, compensation rose from 75 to 87%. Finally, in the most recent study of this type, Rothwell & Stock (229) found that when rats were loaded with from one to three widely spaced meals, their daily intake was reduced in almost perfect compensation (see lines 14–16, Table 4). Similar results were also seen when dogs were chronically given a large fraction of the daily requirement intragastrically (117). However, the rats, unlike the dogs gained from .9 to 2.3 g/day more than controls over 21–30 days (229), and approximately 80% of the gain was fat. Results similar in magnitude to these were also obtained with intravenous nutrient infusions [(1); see line 17, Table 4].

Some of the results above appear to be at variance with a homeostatic theory of food intake control. However, homeostatic theories have been vague about the period over which equilibrium should be achieved. These results need not be considered violations of homeostatic principles if absorption and metabolism of the loaded and ingested food are not completed in the time permitted for response. This time is simply the reciprocal of the subject's energy expenditure. It would be about 20 min for each kcal eaten or loaded in the rat and 1 hr for each 100 kcal consumed by man. Furthermore, in animals subject to only a few hours of feeding (263), lack of perfect compensation could be attributed to the constant stimulus to eat (or removal of satiating effects, whatever these may be) resulting from the sustained energy deficit (in comparison to ad libitum fed animals) that such schedules induce. On the other hand homeostatic theory cannot obviously account for the 18% difference in suppression efficiency between orally and intragastrically loaded food in the experiments of Berkun et al (18) or the failure to see 100% suppression efficiency in other studies. It may be that

Table 4 Effects of nutrient administration on food intake

			Oral loads					Intragastric loads					
				Intake					Intake				
Line	Species	Units	Load size	w/o load	w. load	Diff.[a]	Percentage comp.[b]	Load size	w/o load	w. load	Diff.[a]	Percentage comp.	Reference number
1	Dog	g	200[d]	932	694	238	119	200	1251.0	1308.0	−57	−28	116
2	Dog	g						450	999.5	515.5	484.5	107	116
3	Rat	ml	14.0[d]	19.7	7.1	12.6	90	14.0	19.7	9.6	10.1	72	18
4	Rat	g	4.2[d]	15.0	12.9	2.1	50	4.2	15.0	13.4	1.6	38	263
5	Human	ml	190.0[d]	635.0	476.0	159.0	83						300
6	Human	ml	317.0[d]	635.0	372.0	262.0	83						300
7	Human	ml	698.0[d]	635.0	152.0	483.0	69						300
8	Monkey	kcal	150.0[d]	437.0	273.0	164.0	109	150.0[d]	437.0	273.0	164.0	109	177a
9	Monkey	kcal						300.0[d]	442.0	134.0	306.0	102	177a
10	Monkey	kcal						450.0[d]	446.0	38.0	408.0	91	177a
11	Rat	ml						44.0[e]	72.0	40.0	32.0	72	285
12	Rat	ml						56.0[f]	63.0	21.0	42.0	75	285
13	Rat	ml						36.0	34.8	3.8	31.0	86	215[c]
14	Rat	kcal						31.0[g]	90.7	61.2	29.5	92	229
15	Rat	kcal						45.6[h]	97.2	50.4	46.8	102	229
16	Rat	kcal						59.9[i]	92.4	27.9	64.5	107	229
17	Rat	kcal						49.5[j]	74.5	28.8	45.7	92	1

[a] Difference in intake (without load − with load).
[b] Percentage compensation = difference in intake/load size.
[c] Based on mean data and report that intake was reduced .86 ml for each ml loaded in a meal paired paradigm.
[d] Single preload.
[e] Continuous load via chronically implanted nasogastric tube, 24 hr.
[f] Load with each meal via chronically implanted nasogastric tube, 24 hr.
[g] One load per day via gavage.
[h] Two loads per day via gavage.
[i] Three loads per day via gavage.
[j] Continuous intravenous load, 24 hr.

about one fifth of the satiation that results from eating is contributed by the oropharyngeal stimulation. This percentage approximately matches the 20% reduction in intake seen when rats, and 30% reduction when humans, feed themselves intragastrically (118).

Bulk

As a result of Cannon's (49) influential theory of hunger it has been commonly assumed that a major determinant of satiety and hence the amount of food consumed at a meal is a full stomach. Many observations have been consistent with this view. For example, Janowitz & Grossman (116) found that placing food or bulk in the stomach of a dog 20 min before its normal daily meal inhibited food intake by the same amount. In the rat, Smith & Duffy concluded that "food in the stomach inhibits further eating, but the immediate effect seems attributable to the physical properties (bulk) of the food" [(263), p. 608]. They found that preloads of food and of nonnutritive bulk depressed food intake about equally (see Table 5). Other lines of investigation, however, have led to the conclusion that bulk is not very important in the control of food intake. The many dilution studies previously discussed are examples (see the section on Dietary Dilution and Concentration). Other examples include the effects of bulk preloads in monkeys (176), simultaneous loads of water in man (118), and intragastric infusions of sodium and urea solutions with meals in the rat (268) (see Table 5 for details). Can these disparate findings be reconciled, and what can be concluded about the role of bulk in the control of food intake? Examination of Table 5 reveals several striking inadequacies in our knowledge of the effects of nonnutritive loads or mechanical distension (e.g. by balloon). In each report, only a few (sometimes only one) levels of bulk have been used. It is therefore impossible to determine the functional relationship between bulk and intake. The data suggest that the relation is linear, but not one to one—i.e. before the bulk effect begins to operate it must be in excess of 20% of the normal intake. The second major problem is the effect of the time factor. As Booth (29) has shown, it appears that in the nondeprived rat, bulk (induced by an osmotic load) has an inhibiting effect that lasts up to 2 hr and has disappeared after the fourth hour following a load. On the other hand, Smith & Duffy's (263) work in the deprived rat suggests that the effect lasts for two hours without change (compare lines 6–9 with 12–13 on Table 5). The time course of the effect may interact with deprivation.

A recent study by Deutsch, Gonzalez & Young (73) has attempted to evaluate what intragastric factors led to satiety. When rats were injected with an equal volume of saline as they drank a condensed milk diet, it was found that intake was reduced to about half of what would have been

Table 5 Effects of administration of bulk on food intake

Species	Type of bulk	Mode of administration	Deprivation (hr)	Delay[a]	Duration (hr)	Units		Load size	Amount eaten		Reference number
						Load	Intake		w/o load	w. load	
Dog	gum	gastric fistula	23.25	0	.75	% dry[b]	g	15	841.5	809.0	251
Dog	cellulose	gastric fistula	23.25	0	.75	% dry	g	15	841.5	650.0	251
Dog	balloon	inflation w. water	23.25	0	.75	ml	g	300	892.0	704.5	251
Dog	balloon	inflation w. water	23.25	0	.75	ml	g	500	892.0	578.0	251
Dog	balloon	inflation w. water	23.25	0	.75	ml	g	700[c]	937.0	388.0	251
Rat	kaolin	gavage of 66% slurry	22.00	0	.16	ml	g	10	2.9	2.8	263
Rat	kaolin	gavage of 66% slurry	22.00	0	2.0	ml	g	10	15.0	11.7	263
Rat	kaolin	gavage	22.00	0	.16	ml	g	15	2.9	1.8	263
Rat	kaolin	gavage	22.00	0	2.0	ml	g	15	15.0	9.4	263
Rat	.9% NaCl	nasogastric tube	0.	0	24.0	ml	kcal	47.3	64.4	70.9	268
Rat	1 M urea	nasogastric tube	0.	0	24.0	ml	kcal	46.9	64.8	70.4	268
Rat	1 M urea	gavage	0.	1	1.0	ml	g	5.0	1.7	.2	29
Rat	1 M urea	gavage	0.	1	3.0	ml	g	5.0	1.7	2.0	29
Rat	.9% NaCl	gastric tube	14.0	f	.5	ml	ml	11.7	21.1	11.7	73[d]
Monkey	cellulose	gastric fistula	20.0	0	4.0	ml	kcal	150.0	—	-.8[e]	176
Human	water	gastric tube	3–4	f	.33	ml	ml	370.0	414.0	296.0	118

[a] Interval from load to presentation of food (hr).
[b] % of dry weight of intake without load.
[c] Actually 75% of intake without food for each dog.
[d] Data averaged from all values in experiment 1.
[e] Cellulose suspension (unspecified concentration) was reported to reduce intake by 0.8 kcal.
[f] Load was simultaneous and contingent upon, eating.

expected if volume were the only factor controlling it. Conversely, when 5 ml were removed from the stomach as the rat drank, it overconsumed by almost half as much (7.2) as expected. These findings are consistent with the idea that both nutrient and bulk factors contribute to satiety. Until a quantitative manipulation of the bulk factor alone is made, we will not know exactly how much this factor contributes to the control of food intake. One of the problems in assessing this role is that the volume and contents in the stomach change as the rat eats. In order to circumvent this problem, experimenters have used esophagostomized animals (116), animals with open gastric fistula (258), or animals in which diet is removed as it is drunk (62, 74). In each case, the effects of preloading the stomach with bulk have reduced intake for the duration of sham feeding. However, the data available are insufficient to determine the functional relationship and thereby the mechanism of operation of distension on intake.

Osmotic Effects

Besides filling the gastrointestinal tract, nutrients can exert potential osmotic effects owing to their ability to draw water across semipermeable membranes into the gastrointestinal tract, thus filling it and also inhibiting food intake by temporarily dehydrating the rest of the body (68). Schwartzbaum & Ward (245) showed that food intake was depressed as much by stomach loads of hypertonic sodium chloride solutions as by equiosmotic glucose. Jacobs (115) pointed out that the two substances do not produce equivalent thirst effects and suggested that different inhibitory mechanisms were involved. This suggestion received some confirmation by Yin et al (311), who showed in an 8-hr test that intragastric glucose loads (10 ml, 45%) continued to suppress intake even when the rat was hydrated by the intravenous route, but that the suppression of intake induced by equiosmotic sodium chloride (10 ml, 8.1%) loads was almost totally abolished by intravenous water. This confirmation cannot be considered complete because it does not address the question of osmotic effects within the first few hours. Booth (29) showed that glucose, equiosmotic urea, and 3-o-methyl glucose—all poor inducers of thirst—have equal suppressing effects on food intake for the first two hours after a 1 M load of 5 ml. In the third hour only glucose continues to suppress intake. Booth suggests that inhibition by glucose in the first hour is mediated by a chemoreceptor with which 3-o-methyl glucose has a less effective interaction. It is therefore clear that at best osmotic effects are short-lived, but it is not clear whether the initial suppression by glucose is chemospecific, osmotic, or physical.

Energy vs Specific Nutrients

Since other reviewers (4, 30, 40, 203, 295) have provided evidence for and against the classic homeostatic hypotheses, we proceed directly to the ques-

tion of whether chemospecific or energy-related properties of nutrients control intake. Because the macronutrients have differing sensory qualities, we consider only studies in which the sensory contributions from the oropharynx have been effectively eliminated (34, 35, 91) either by anesthesia, disguise of taste and flavor, or loading of nutrients directly into the circulation or digestive tract. Because energy regulation requires time for food to be absorbed and metabolized before its energy yield could be sensed directly, as either heat or stored nutrient, experiments bearing on this question must last long enough for these processes to occur. The longer the experiment lasts, the more likely the control of food intake by energy regulation will be confirmed. We therefore consider the longest studies first.

Liu & Yin (161) chronically loaded rats intragastrically with either 45% glucose solution or Crisco™ (fat with a 3:1 ratio of unsaturated to saturated fatty acids) in equicaloric amounts (27 kcal/day) for 5 weeks. Food intake was reduced in proportion to the calories loaded throughout the period, and body composition was no different between loading conditions when determined 1 week after termination of the loading. These results support an energy regulation hypothesis. Rothwell & Stock (229) using a similar procedure for only 30 days, but employing butter (3:5 ratio of unsaturated to saturated fatty acids) instead of Crisco™, reported that compensation was only 48% efficient, although when their animals were loaded with an equicaloric volume of a complete diet, suppression was 92% effective (see Table 4). They suggested that because of imbalances in dietary nutrients induced by the fat loads rats were eating to obtain sufficient amounts of other nutrients. Geliebter (92) reported in a longer study (6 weeks) that daily loads of either butter, corn oil, sucrose, or albumin gave nonsignificant differences in food intake across nutrients, and nonsignificant differences in body weight gain and Lee index. He did, however, note a persistent reduction in intake after protein loads 3.5 hr after the load.

These results suggest that any shorter term studies that showed differences in intake suppression across macronutrients (90, 91, 202) would not necessarily preclude adjustment of intake according to an energy balance regulation mechanism, but could be explained as a result of transient chemospecific effects on satiety. Examples of both energy regulatory and chemospecific effects have been found in short-term experiments. Energy regulation is favored by Booth (28), who found that when allowance was made for absorption and metabolism after a load, before food is presented, small nutrient loads (about the size of a normal meal) in otherwise undeprived rats depressed food intake by amounts almost equal to their metabolizable energy. When preabsorptive effects were examined, Booth (28) found a wide variety of intakes in the first hour of access after a 1 hr delay. Intake was least after glucose (0.9 g), highest after glycerol (2.4 g) and oleate (2.1

g) and intermediate after the amino acids valine (1.6 g) and lactate (1.4 g). Geary (90), however, found that suppression efficiency was greater for protein (1.51 kcal reduction in intake per kcal loaded) than glucose (.87) after 12 hr, but the difference was smaller after 24 hr (1.32 for protein and .81 for glucose). The difference from the results of Booth (28) could be attributed to use of proteins rather than amino acids in Geary's (90) study and to the fact that early effects of proteins were included in the 12 hr measures. The convergence of the suppression ratios at 24 hr suggests that longer times would be needed to adequately refute the hypothesis that enhanced nutrient-specific satiety effects of protein are eventually balanced by an energy regulatory mechanism that restores intake. Similar short-term effects of protein on human appetite have been reported (35).

Other studies suggest that the effects of nutrient administration interact with deprivation and possibly with the time of testing. For example, Panksepp (202) found no differences in the effects of equicaloric fat, carbohydrate, and protein loads, but his animals were 12 hr deprived and only tested for 0.5 hr in the light. The half-hour test probably only picks up gastric filling effects, and the animals may be less sensitive to the nutrient effects because of the deprivation, since Booth & Jarman (36) have shown that intake-suppressing effects of small amounts of glucose disappear after 4 hr of deprivation. Panksepp (202) did, however, find a 3.6 g larger suppression of intake following administration of protein than fat or carbohydrate in the first half hour of access to food after a period of spaced loads of 6 meals over 30 hr without other food available. Over the next 24 hr this difference was completely made up. He also found that fat loads suppressed intake less than did carbohydrate or protein loads after a 1-hr delay but not a 3-hr delay from load to eating in rats that were 3.5 hr deprived and tested in the light phase. These apparently conflicting results will not be resolved until we know more about the interaction of nutrient administration with metabolic effects of deprivation and light-dark cycle [see (151) for discussion of these effects]. Problems of interactions of nutrient administration with other factors abound in the long-term studies as well. Differences between the results of Geliebter (92) and Rothwell & Stock (229) could be attributed to the age of the animals, the schedule of nutrient administration, and/or duration of the experiment. Our answer to the question of whether intake is controlled by a nutrient-specific or an energy-regulatory mechanism must be tentative. It appears that in the short run satiety is under chemospecific control, in which the effectiveness per calorie increases in the order: fats, carbohydrates, and proteins. In the long run, when these nutrients are metabolized they exert their effects on food intake by means of their energy yield.

Nonnutritive Influences on the Outcome of Nutrient-Administration Experiments

In addition to the examples of nonnutritive effects presented above, there are several other important illustrations of the interaction of nutrient administration with other variables. The interaction between administration site and deprivation is a case in point: Isotonic glucose infusion suppressed food intake when injected duodenally into nondeprived rabbits or into the hepatic portal vein of deprived rabbits, but the same infusion had no effect when infused into the duodenum of a deprived rabbit or the hepatic portal vein of a nondeprived rabbit (291). The explanation for these findings, consistent with Russek's hepatostatic theory (236), is that duodenal infusion released more gut glucagon than did hepatic portal infusion, thereby raising the intrahepatic concentration of glucose in the nondeprived rabbit and inhibiting a vagally mediated activating signal (197, 291). In the deprived rabbit, glycogen is depleted and thus glucagon released by the duodenal infusion would have no effect. In the nondeprived rabbit, hepatic-portal infusion does not raise the glucose level in hepatic cells because there is already a high carbohydrate level in them, presumably preventing further uptake of glucose necessary to raise the glucose concentration within the cells. Further evidence for glucagon's role in mediating this effect has been obtained (289–290, 293). The importance of route of administration was also shown by the results of Snowdon (268), who found that meal-contingent duodenal infusion of hyperosmotic substances as well as nutrients reduced spontaneous meal size but did not reduce total nutrient intake, while only nutritive substances reduced meal size when infused into the stomach. These results suggested a duodenal rather than gastric locus for the osmotic inhibition of feeding.

The importance of nutritional status (deprived vs nondeprived) was shown by Baile et al (13), who found that glucose inhibited food intake in monkeys when infused intragastrically along with a meal (thus the animal was not in the deprived state), but not when it was given during a half-hour period preceding the meal, after a 22-hr fast. Suppression by preloaded glucose in deprived monkeys was observed, however, by McHugh & Moran (176). The latter believe that differences in the results are due to differences in the length of time food was available and the restraint imposed in the earlier (13) study. In man, Booth et al (34) have shown that a glucose load 15 min before a meal suppressed intake in proportion to the calories in the load, but did not do so if given just before the meal. On the other hand, intravenous infusion of glucose alone (21, 100) or along with insulin (305) failed to either increase or decrease food intake in man. In the rat, intravenous addition of insulin to glucose infusion did improve the suppression

efficiency (191), but this effect could be attributable to the higher basal feeding level against which the results were compared when insulin alone was administered. It is clear that factors other than the kind of nutrients must be considered in the interpretation of the results of nutrient administration.

MECHANISMS

Much of the current work on the physiology of food intake control concerns the mechanisms underlying the phenomena and experimental results described above. Some of these, such as the hepatostatic hypothesis and gastrointestinal controls, have already been described. We now provide an overview of hormonal and vagal mediators of satiety, humoral and neural controls of the chronic effects of body weight on food intake, and the glucoprivic control of hunger. The reader may wish to consult one of the many recent symposium proceedings (51, 145, 195) or books (33, 241, 278) for further information.

Mechanisms of Satiety

We consider first the signals by which nutrient ingestion tells the central nervous system to terminate feeding. Both Kraly & Smith (142) and Deutsch and colleagues (74) have shown, using a pyloric noose to prevent outflow from the stomach to intestine, that the oropharynx and stomach together provide signals sufficient to induce satiety. Distension and nutrients induce satiety by different mechanisms, since vagotomy abolishes the response to distension but not to nutrients (96, 141). The stomach may also contain receptors for fat, since Deutsch & Gonzalez (72) found that intake of a 50% fat emulsion was the same whether the pylorus was occluded by cuff or not; intake of the emulsion increased when some of it was removed as they drank but remained the same when saline was injected as they drank. Unfortunately, a critical alternative condition—infusion of saline while the animals drank the emulsion with the pyloric cuff on—was not studied. Thus fat could have inhibited ingestion by a duodenal mechanism in the cuff-off condition while distension of the stomach inhibited it in the cuff-on condition.

Satiety signals can also arise from the intestine as shown by the effects of nutrient infusions into it. These effects could be mediated by one of several hormones released from the gut, stomach, or pancreas (259, 308). The hormone most thoroughly studied is cholecystokinin (CCK) (261). The target of its activity is probably not the brain but a vagally innervated structure, since vagotomy blocks its effect in the rat (260). Since CCK did reduce food intake when infused (though it did not when injected as a bolus) into the cerebral ventricles of sheep (69), there may be species differences

in its mechanisms of action. Rats do not respond to intraventricular CCK (69). If the mechanisms of action are different in the two species, vagotomy should not affect the response to peripherally administered CCK in sheep. Administration of several other peptides found in the gut also led to reduction in food intake [see (259, 308) for reviews].

The neurotransmitters involved in the control of food intake are also being studied [see (147) for an encyclopedic review]. Feeding can be stimulated by norepinephrine injections into the paraventricular nucleus [apparently the target or origin of fibers whose damage leads to hyperphagia (187)] by means of an alpha-adrenergic mechanism (146). Feeding is inhibited by norepinephrine injection into the perifornical area of the hypothalamus [whose damage results in aphagia (6)] by means of a beta-adrenergic mechanism (148). When nutrients were infused into the duodenum, synaptic release of norepinephrine was enhanced at lateral sites where norepinephrine injections did not induce feeding [but suppressed it in other studies (148)], and synaptic norepinephrine release was suppressed at medial sites where norepinephrine injections enhanced feeding (188). Because norepinephrine is an inhibitory transmitter, the simplest hypothesis consistent with earlier lesion and stimulation studies is that norepinephrine elevation in the medial area suppresses "satiety" neurons by means of an alpha-adrenergic mechanism; feeding is then suppressed by a duodenally activated mechanism that increases norepinephrine in the lateral area, thereby inhibiting "feeding" neurons by means of a beta-adrenergic mechanism.

Serotonin is also probably involved in inhibition of food intake [see (299) for recent evidence and a brief review]. This inhibition may be linked to carbohydrate (82, 310), but probably not to protein, ingestion (210).

The latest in the series of neurotransmitters involved with feeding are the endogenous opioids (166, 308). Feeding is enhanced by the administration of beta-endorphin (97, 130) and its agonist, D-ala^2-metenkephalinimide (12) and is decreased by the opiate antagonist naloxone (167). However, it is not clear whether this reduction in appetitive behavior is general or specific to food intake, because naloxone reduces several appetitive behaviors (200, 271). The possibility that the endorphin system is specifically involved in the overeating of palatable foods or in the weight gain ensuing from it was suggested by the finding that naltrexone, another opiate antagonist, reduced food intake in animals that were eating an array of palatable foods but not in rats that were eating laboratory chow (10).

Mechanisms For Detecting Energy Deficits

No one has ever isolated a factor that directly induces appetite. However, food intake can be stimulated by administration of insulin (163), 2-deoxy-D-glucose [2-DG (257, 286)], and 5-thioglucose [5-TG (222)]. All of these substances result in reduction of glucose utilization in the brain, the last two

in all glucose utilizing cells. The eating effect can be blocked or attenuated by administering metabolic fuels that can be used by liver or brain in the case of insulin administration (234, 276), or by the brain alone in the case of 2-DG administration (275). Therefore these treatments probably induce eating not by glucoprivation but rather by energy privation. The eating response is probably linked not directly to insufficiency of circulating fuels but rather to depletion of an organ. For example, increased eating persists in insulin- or 2-DG-treated animals even after 6 hr without food, at a time when all circulating parameters have returned to normal (221). One possible locus for this effect is the liver, since its glycogen stores remain depleted (85, 98), although not empty (221), until feeding is allowed and since fructose administration blocks the increased eating only in hepatic-vagally intact animals (98). The other possibility is the brain, since its norepinephrine turnover (which would inhibit "satiety" neurons) remains high unless feeding occurs (16). The site for the action of glucoprivic stimuli may be the caudal hindbrain, since injections of 5-TG into the fourth ventricle increased food intake (223, 256).

Mechanisms of Long-Term Control

On the basis of initial hyperphagia and weight gain after ventromedial hypothalamic (VMH) damage, and subsequent reduction in intake after weight had stabilized, Kennedy (128) proposed that a circulating factor correlated with the size of the fat depots suppressed intake in the obese animal. He further proposed that the ventromedial satiety mechanism was directly or indirectly sensitive to the state of the energy reserves so that after VMH damage a greater stimulus was required to inhibit eating (129). Evidence for a circulating factor came from parabiosis experiments in which two animals were sewn together so that they shared a fraction of a common blood supply. When one member of the pair was overfed, the partner ate less and became emaciated (109, 206).

The identity of the circulating factor remains a mystery, but recent evidence suggests it is either insulin in the cerebrospinal fluid (213) or glycerol (67). Cerebrospinal insulin level has been shown to covary with plasma level (307), but fluctuations are greatly damped in the CSF. Plasma insulin covaries in turn with the state of the fat stores (19). Infusion of insulin into the cerebral ventricles of baboons resulted in a loss in body weight and reduction in food intake (306). Glycerol has been proposed as a signal of fat store size because fat catabolism yields it quantitatively and it is not reutilized by that tissue. Administration of glycerol by various routes inhibits food intake and induces weight loss (94, 101, 301). Other metabolites share this ability to a lesser extent when injected into the brain (66), and the glycerol effect is most pronounced in the vicinity of the third ventricle (67).

Not all investigators agree with the hypothesis that the function of the ventromedial hypothalamic area is to detect the size of body energy stores and control food intake accordingly. The interpretation of the ventromedial lesion syndrome has been controversial since its discovery. Sclafani (247) has recently summarized the evidence favoring a primary hyperphagia, and Bray et al (41) and Powley (214) have summarized evidence for primary endocrine and autonomic disturbances that could lead to hyperphagia by means of increased insulin secretion. It has also been suggested that the two sequelae of the lesion (hyperphagia and hyperinsulinemia) are independent effects of damage to overlapping systems (15), because each can be induced in the absence of the other.

Further evidence for this independence of effects comes from recent work on vagotomy in rats with ventromedial hypothalamic damage (either by lesion or knife cut). Cox & Powley (57) have definitively shown that a doubling of body fat is attained after VMH lesions when food intake is limited, by a special infusion pair-feeding paradigm, to the pattern and amount consumed by a neurologically intact rat. This effect is blocked by vagotomy (58). However, it should be noted that the weight gain of animals with restricted feeding was considerably less (1.3 g/day) than it was on a comparable diet eaten ad libitum [5.4 g/day (15)]. Therefore, although VMH lesions predispose toward obesity, hyperphagia greatly enhances it. The argument over which sequela (hyperphagia or hyperinsulinemia) of VMH damage is "primary" for obesity is a sterile one. This conclusion is further shown by the work of Sawchenko and colleagues (242), who found that the coeliac branch of the vagus must remain intact for increased weight gain to occur after VMH damage only on a chow and not on a high-fat diet (243). On high-fat diets vagotomy is less effective in attenuating weight gain and hyperphagia after VMH damage than it is on high-carbohydrate diets (248). These results are consistent with the hypothesis that vagotomy may reduce obesity by suppressing insulin secretion, which is necessary for carbohydrate, but not fat, utilization; but this hypothesis cannot account for persistence of hyperphagia in VMH-lesioned diabetic rats (83, 297, 313), whose insulin secretion is severely impaired. Such animals, of course, fail to become obese on high carbohydrate diets. It is still a mystery why hyperphagia is attenuated in VMH-damaged animals with coeliac vagotomy (242) on low fat diets while hyperphagia persists in the VMH-damaged diabetic animal, since both animals have impaired insulin secretion.

CONCLUSIONS

Given the array of factors that influence feeding behavior and the variety of theories proposed to account for them, is it possible to effect a synthesis

that is both explanatory and predictive? The multiplicity of signals and sites involved in the control of intake makes it difficult, if not impossible, to accept simplistic explanations such as dual centers in the brain or primary control by a single organ such as the stomach or liver. Understanding amid such complexity is best gained by expressing relationships among variables in mathematical terms and testing hypotheses by comparing computed outcomes of alternatives against empirically obtained data. However, since many readers are not familiar with this approach, we attempt here to summarize verbally what has been discovered.

Search for food is initiated when certain portions of the brain are activated by (*a*) disinhibition of its spontaneous activity as a result of removal of inhibitory input from either the blood stream or cerebrospinal fluid, and/or (*b*) increased excitation from neural or humoral signals from the liver. These inputs influence the brain cells by means of specific neurotransmitters. The same brain cells are also influenced in their activity by direct or indirect detection of fat stores, possibly through links with circumventricular organs or by combination with the normal changes in metabolism believed to influence feeding. Once food is located, feeding is initiated under the control of cells in overlapping but possibly anatomically distinct regions and is maintained by "reward-sensitive" neurons whose activity is gated as a result of disinhibition (i.e. these cells will only be active when the animal is in a "hunger" state). As feeding proceeds, inhibitory inputs impinge on the "reward" cells and at a certain level of inhibition they will no longer be activated by the sensory qualities of the food. Eating of that particular food would then stop, although other foods could still activate the reward neurons, thereby accounting for sensory-specific satiety (225). Absolute satiety would be evidenced by behavioral quiescence and neural inhibition of the regions responsible for search and initiation of eating. Because learning also contributes to control of food intake (32), we suggest that the response of reward neurons to the stimulus qualities of food is modified by postingestive events, and that this modification contributes to the activity of the reward neurons by either enhancing their activity if the postingestive effect results in reward (satiety), or reducing their activity if it results in punishment (illness). This scheme is no doubt filled with flaws but is proposed as a challenge on which to improve.

Finally, we would like to note that the burden of review would be considerably eased and information would be easier to digest if data from comparable methods were presented in comparable units. It is impossible to compare results from such widely divergent units as percentages of control values, percentages of body weights, difference scores across conditions, and simple weight of food consumed. To improve the situation it is suggested that intake data be reported in the units in which they are collected. An

author who wishes to convert these data to some other format could then do so separately. When there is more than one source of variance (e.g. animals and times—i.e. repeated observations on an animal at intervals, or replicate observations), analysis of variance would allow the reader to determine how much variability to expect from each source when experiments are replicated or extended. Enough details of the experimental conditions should be presented to enable replication. At a minimum these should include species, sex, strain, breeder, age, and weight of the animal; conditions of illumination, temperature, housing or restraint; macronutrient content of the diet and its energy density. As our ability to collect data increases, owing to automatic weighing and other instruments, our ability to understand them will decline unless we adopt a strategy to organize them. Quantitative data in comparable units are amenable to computerized storage and retrieval. Perhaps if the data are published in a more quantitatively comparable way than they are at present, the next generation of reviews in this field will be prepared with the aid of computerized data bases.

Literature Cited

1. Adair, E. R., Miller, N. E., Booth, D. A. 1968. Effects of continuous intravenous infusion of nutritive substances on consummatory behavior in rats. *Behav. Biol A* 2:25–37
2. Adolph, E. F. 1943. *Physiological Regulations* Lancaster: Cattell. 502 pp.
3. Adolph, E. F. 1947. Urges to eat and drink in rats. *Am. J. Physiol.* 151:110–25
4. Anand, B. K. 1961. Nervous regulation of food intake. *Physiol. Rev.* 41:677–708
5. Anand, B. K. 1967. Central chemosensitive mechanisms related to feeding. In *Handbook of Physiology,* Section 6, *Alimentary Canal,* Vol. 1. *Food and Water Intake,* ed. C. F. Code, pp. 249–63. Washington DC: Am. Physiol. Soc.
6. Anand, B. K., Brobeck, J. R. 1951. Hypothalamic control of food intake in rats and cats. *Yale J. Biol. Med.* 24:123–40
7. Andik, I., Bank, J., Moring, I., Szegvari, G. Y. 1954. Effects of exercise on the intake and selection of food in the rat. *Acta Physiol. Hung.* 5:457–61
8. Antelman, S. M., Szechman, H. 1975. Tail-pinching induces eating in sated rats which appears to depend on nigrostriatal dopamine. *Science* 189:731–33
9. Antin, J., Gibbs, J., Holt, J., Young, R. C., Smith, G. P. 1975. Cholecystokinin elicits the complete behavioral sequence of satiety in rats. *J. Comp. Physiol. Psychol.* 89:784–90
10. Apfelbaum, M., Mandenoff, A. 1981. Naltrexone suppresses hyperphagia induced in the rat by a highly palatable diet. *Pharmacol. Biochem. Behav.* 15:89–91
11. Armstrong, S., Coleman, G., Singer, G. 1980. Food and water deprivation: Changes in rat feeding, drinking, activity, and body weight. *Neurosci. Biobehav. Rev.* 4:377–402
12. Baile, C. A., Keim, D. A., Della-Fera, M. A., McLaughlin, C. L. 1981. Opiate antagonists and agonists and feeding in sheep. *Physiol. Behav.* 26:1019–23
13. Baile, C. A., Zinn, W., Mayer, J. 1971. Feeding behavior of monkeys: Glucose utilization rate and site of glucose entry. *Physiol. Behav.* 6:537–41
14. Bare, J. K., Cicala, G. A. 1960. Deprivation and time of testing as determinants of food intake. *J. Comp. Physiol. Psychol.* 53:151–54
15. Becker, E. E., Kissileff, H. R. 1974. Inhibitory controls of feeding by the ventromedial hypothalamus. *Am. J. Physiol.* 226:383–96
16. Bellin, S., Ritter, S. 1981. Insulin-induced elevation of hypothalamic norepinephrine turnover persists after glucorestoration unless feeding occurs. *Brain Res.* 217:327–37

17. Bellinger, L. L. 1981. Commentary on the "Current status of the hepatostatic theor of food intake control." *Appetite* 2:144–45
18. Berkun, M. M., Kessen, M. L., Miller, N. E. 1952. Hunger-reducing effects of food by stomach fistula versus food by mouth measured by a consummatory response. *J. Comp. Physiol. Psychol.* 45:550–54
19. Bernstein, I. L., Lotter, E. C., Kulkosky, P. J., Porte, D. Jr, Woods, S. C. 1975. Effect of force-feeding upon basal insulin levels of rats. *Proc. Soc. Exp. Biol. Med.* 150:546–48
20. Bernstein, I. L., Zimmerman, J. C., Czeisler, C. A., Weitzman, E. D. 1981. Meal patterns in free-running humans. *Physiol. Behav.* 27:621–23
21. Bernstein, L. M., Grossman, M. I. 1956. An experimental test of the glucostatic theory of the regulation of food intake. *J. Clin. Invest.* 35:627–33
22. Bjorntorp, P., Yang, M.-U. 1982. Refeeding after fasting in the rat I. Effects on body composition and food efficiency. *Int. J. Obesity.* In press
23. Blass, E. M., Kraly, F. S. 1974. Medial forebrain bundle lesions: specific loss of feeding to decreased glucose utilization in rats. *J. Comp. Physiol. Psychol.* 86:679–92
24. Bobroff, E. 1981. Independent measure of palatability correlates with initial rate of eating in men. Presented at Eastern Psychol. Assoc., 52nd, New York
25. Bolles, R. C. 1980. Historical note on the term "appetite." *Appetite* 1:3–6
26. Booth, D. A. 1972. Caloric compensation in rats with continuous or intermittent access to food. *Physiol. Behav.* 8:891–99
27. Booth, D. A. 1972. Conditioned satiety in the rat. *J. Comp. Physiol. Psychol.* 81:457–71
28. Booth, D. A. 1972. Postabsorptively induced suppression of appetite and the energostatic control of feeding. *Physiol. Behav.* 9:199–202
29. Booth, D. A. 1972. Satiety and behavioral caloric compensation following intragastric glucose loads in the rat. *J. Comp. Physiol. Psychol.* 78:412–32
30. Booth, D. A. 1976. Approaches to feeding control. In *Appetite and Food Intake,* ed. T. Silverstone, pp. 417–78. Berlin: Abakon. 497 pp.
31. Booth, D. A. 1977. Appetite and satiety as metabolic expectancies. In *Food Intake and Chemical Senses,* ed. Y. Katsuki, M. Sato, S. F. Takagi, Y. Oomura, pp. 317–30. Baltimore: University Park Press. 614 pp.
32. Booth, D. A. 1978. Acquired behavior controlling energy intake and output. In *Psychiatric Clinics of North America,* ed. A. J. Stunkard, 1:545–79. Philadelphia: W. B. Saunders 732 pp.
33. Booth, D. A., ed. 1978. *Hunger Models Computable Theory of Feeding Control.* NY: Academic. 478 pp.
34. Booth, D. A., Campbell, A. T., Chase, A. *1970.* Temporal bounds of postingestive glucose-induced satiety in man. *Nature* 228:1104–5
35. Booth, D. A., Chase, A., Campbell, A. T. *1970.* Relative effectiveness of protein in the late stages of appetite suppression in man. *Physiol. Behav.* 5:1299–1302
36. Booth, D. A., Jarman, S. P. 1976. Inhibition of food intake in the rat following complete absorption of glucose delivered into the stomach, intestine, or liver. *J. Physiol. 259:501–22*
37. Booth, D. A., Lovett, D., McSherry, G. M. 1972. Postingestive modulation of the sweetness preference gradient in the rat. *J. Comp. Physiol. Psychol.* 78:485–512
38. Booth, D. A., Mather, P. 1978. Prototype model of human feeding, growth, and obesity. See Ref. *33,* pp. *279–322*
39. Borer, K. T., Rowland, N., Mirow, A., Borer, R. C., Kelch, R. P. 1979. Physiological and behavioral responses to starvation in the golden hamster. *Am. J. Physiol.* 236:E105–12
40. Bray, G. A. 1976. Peripheral metabolic factors in the regulation of feeding. See Ref. 30, pp. 141–76
41. Bray, G. A., Inoue, S., Nishizawa, Y. 1981. Hypothalamic obesity. The autonomic hypothesis and the lateral hypothalamus. *Diabetologia* 20: (Suppl.) 366–77
42. Bray, G. A., York, D. A. 1972. Studies on food intake in genetically obese rats. *Am. J. Physiol.* 223:176–79

42a. Brobeck, J. R. 1955. Neural regulation of food intake. *Ann. NY Acad. Sci. 63* (art 1): 44–55

43. Brobeck, J. R. 1960. Food and temperature. *Rec. Adv. Horm. Res.* 16:439–59
44. Brobeck, J. R. 1965. Exchange, control, and regulation. In *Physiological Controls and Regulations,* ed. W. S. Yamamoto, J. R. Brobeck, pp. 1–13. Philadelphia: W. B. Saunders. 362 pp.
45. Brobeck, J. R. 1981. Models for analyzing energy balance in body weight regulation. In *The Body Weight Regulatory System: Normal and Disturbed Mecha-*

nisms, ed. L. A. Cioffi, W. P. T. James, T. B. Van Itallie, pp. 1–9. NY: Raven Press. 380 pp.
46. Brobeck, J. R., Tepperman, J., Long, C. N. H. 1943. Experimental hypothalamic hyperphagia in the albino rat. *Yale J. Biol. Med.* 15:831–53
47. Cabanac, M., Duclaux, R., Spector, N. H. 1971. Sensory feedback in regulation of body weight: Is there a ponderostat? *Nature* 229:125–27
48. Campbell, R. G., Hashim, S., Van Itallie, T. B. 1971. Studies of food-intake regulation in man, responses to variations in nutritive density in lean and obese subjects. *N. Engl. J. Med.* 285:1402–7
49. Cannon, W. B., Washburn, A. L. 1912. An explanation of hunger. *Am. J. Physiol.* 29:444–54
50. Carlisle, H. J., Stellar, E. 1969. Caloric regulation and food preference in normal, hyperphagic and aphagic rats. *J. Comp. Physiol. Psychol.* 69:107–14
51. Cioffi, L. A., James, W. P. T., Van Itallie, T. B., eds. 1981. See Ref. 45.
52. Cohn, C., Joseph, D. 1962. Influence of body weight and body fat on appetite of "normal" lean and obese rats. *Yale J. Biol. Med.* 34:598–607
53. Collier, G. H. 1981. An ecological analysis of motivation. In *Analysis of Motivational Processes,* ed. F. Toates, T. Halliday, pp. 125–51. NY: Academic
54. Collier, G., Hirsch, E., Hamlin, P. H. 1972. The ecological determinants of reinforcement in the rat. *Physiol. Behav.* 9:705–16
55. Collier, G., Hirsch, E., Kanarek, R. 1978. The operant revisited. In *Handbook of Operant Psychology,* ed. W. K. Honig, J. E. R. Staddon, pp. 28–52. Englewood Cliffs, NJ: Prentice Hall
56. Collier, G., Leshner, A. I., Squibb, R. L. 1969. Dietary self-selection in active and non-active rats. *Physiol. Behav.* 4:79–82
57. Cox, J. E., Powley, T. L. 1981. Intragastric pair feeding fails to prevent VMH obesity or hyperinsulinemia. *Am. J. Physiol.* 240:E566–72
58. Cox, J. E., Powley, T. L. 1981. Prior vagotomy blocks VMH obesity in pair-fed rats. *Am. J. Physiol.* 240:E573–83
59. Cowgill, G. R. 1928. The energy factor in relation to food intake: Experiments in the dog. *Am. J. Physiol.* 85:45–64
60. Cruce, J. A. F., Greenwood, M. R. C., Johnson, P. R., Quartermain, D. 1974. Genetic versus hypothalamic obesity: Studies of intake and dietary manipulations in rats. *J. Comp. Physiol. Psychol.* 87:295–301
61. Cumming, M., Morrison, S. D. 1960. The total metabolism of rats during fasting and refeeding. *J. Physiol.* 154:219–43
62. Davis, J. D., Campbell, C. S. 1973. Peripheral control of meal size in the rat: Effect of sham feeding on meal size and drinking rate. *J. Comp. Physiol. Psychol.* 83:379–87
63. Davis, J. D., Collins, B. J., Levine, M. W. 1976. Peripheral control of meal size: interaction of gustatory stimulation and postingestional feedback. *In Hunger: Basic Mechanisms and Clinical Implications,* ed. D. Novin, W. Wyricka, G. A. Bray, pp. 395–408. NY: Raven Press
64. Davis, J. D., Collins, B. J., Levine, M. W. 1978. The interactions between gustatory stimulation and gut feedback in the control of ingestion of liquid diets. See Ref. 33, pp. 109–42
65. Davis, J. D., Levine, M. W. 1977. A model for the control of ingestion. *Psychol. Rev.* 84:379–412
66. Davis, J. D. Wirtshafter, D., Asin, K., Brief, D. 1981. Sustained intracerebroventricular infusion of brain fuels reduces body weight and food intake in rats. *Science.* 212:81–83
67. Davis, J. D., Wirtshafter, D., Asin, K., Brief, D. 1983. Sustained intracerebroventricular infusion of glycerol causes body weight loss in rats. *Am. J. Physiol.* In press
68. Deaux, E., Kakolewski, J. W. 1971. Character of osmotic changes resulting in the initiating of eating. *J. Comp. Physiol. Psychol.* 74:248–53
69. Della-Fera, M. A., Baile, C. A. 1980. Cerebral ventricular injections of CCK-octapeptide and feed intake: The importance of continuous injection. *Physiol. Behav.* 24:1133–38
70. Deutsch, J. A. 1978. The stomach in food satiation and the regulation of appetite. *Prog. Neurobiol.* 10:135–53
71. Deutsch, J. A. 1980. Bombesin—satiety or malaise. *Nature* 285:592
72. Deutsch, J. A., Gonzalez, M. F. 1981. Gastric fat content and satiety. *Physiol. Behav.* 26:673–76
73. Deutsch, J. A., Gonzalez, M. F., Young, W. G. 1980. Two factors control meal size. *Brain Res.* Bull. 5: (Suppl 4) 55–57
74. Deutsch, J. A., Young, W. G., Kalogeris, T. J. 1978. The stomach signals satiety. *Science* 201:165–67

75. Dufort, R. H., Wright, J. H. 1962. Food intake as a function of duration of food deprivation. *J. Psychol.* 53:465–68
76. Edholm, O. G., Fletcher, J. G., Widdowson, E. M., McCance, R. A. 1955. The energy expenditure and food intake of individual men. *Brit. J. Nutr.* 9:286–300
77. Epstein, A. N. 1960. Reciprocal changes in feeding behavior produced by intrahypothalamic chemical injections. *Am. J. Physiol.* 199:969–74
78. Epstein, A. N. 1967. Oropharyngeal factors in feeding and drinking. See Ref. 5, pp. 197–218
79. Epstein, A. N., Nicolaidis, S., Miselis, R. 1975. The glucoprivic control of food intake and the glucostatic theory of feeding behavior. In *Neural Integration of Physiological Mechanisms and Behavior,* ed. G. J. Mogenson, F. R. Calaresu, pp. 148–68. Toronto: Univ. Toronto Press. 442 pp.
80. Epstein, A. N., Teitelbaum, P. 1967. Specific loss of the hypoglycemic control of feeding in recovered lateral rats. *Am. J. Physiol.* 213:1159–67
81. Faust, I. M. 1981. Signals from adipose tissue. See Ref. 45, pp. 39–44
82. Fernstrom, J. D., Wurtman, R. J. 1971. Brain serotonin content: increase following ingestion of a carbohydrate diet. *Science* 174:1023–25
83. Friedman, M. I. 1972. Effects of alloxan diabetes on hypothalamic hyperphagia and obesity. *Am. J. Physiol.* 222:174–78
84. Friedman, M. I. 1978. Hyperphagia in rats with experimental diabetes mellitus: A response to a decreased supply of utilizable fuels. *J. Comp. Physiol. Psychol.* 92:109–17
85. Friedman, M. I., Granneman, J. 1982. Food intake and peripheral metabolic factors after recovery from insulin induced hypoglycemia. *Am. J. Physiol.* In press
86. Friedman, M. I., Stricker, E. M. 1976. The physiological psychology of hunger: a physiological perspective. *Psychol. Rev.* 83:409–31
87. Friend, B. W. 1973. Self-selection of feeds and water by unbred gilts. *J. Animal Sci.* 37:1137–41
88. Gale, S. K., Van Itallie, T. B., Faust, I. M. 1981. Effects of palatable diets on body weight and adipose tissue cellularity in the adult obese female Zucker rat (fa/fa). *Metabolism* 30:105–10
89. Gasnier, A., Mayer, A. 1939. Recherches sur la régulation de la nutrition. III. Mechanisms régulateurs de la nutrition et intensité du métabolisme. *Ann. Physiol. Physiochim. Biol.* 15:186–94
90. Geary, N. 1979. Food intake and behavioral caloric compensation after protein repletion in the rat. *Physiol. Behav.* 23:1089–98
91. Geliebter, A. A. 1979. Effects of equicaloric loads of protein, fat, and carbohydrate on food intake in the rat and man. *Physiol. Behav.* 22:267–73
92. Geliebter, A. A. 1980. Effects of long-term loading of isocaloric macronutrients on food intake. Paper presented at Meet. East. Psychol. Assoc., April, 1980, New York
93. Gibbs, J., Smith, G. P. 1980. Reply to Deutsch. *Nature* 285:592
94. Glick, Z. 1980. Food intake of rats administered with glycerol. *Physiol. Behav.* 25:621–26
95. Glick, Z., Modan, M. 1977. Behavioral compensatory responses to continuous duodenal and upper ileal glucose infusion in rats. *Physiol. Behav.* 19:703–5
96. Gonzalez, M. F., Deutsch, J. A. 1981. Vagotomy abolishes cues of satiety produced by gastric distension. *Science* 212:1283–84
97. Grandison, L., Guidotti, A. 1977. Stimulation of food intake by muscimol and beta endorphin. *Neuropharmacol.* 16:533–36
98. Granneman, J., Friedman, M. I. 1982. Cerebral and peripheral factors in the control of food intake following acute effects of 2-deoxy-D-glucose injection. *Am. J. Physiol.* In press
99. Grinker, J. G. 1978. Obesity and sweet taste. *Am. J. Clin. Nutr.* 31:1078–87
100. Grinker, J., Cohn, C., Hirsch, J. 1971. The effects of intravenous administration of glucose, saline, and mannitol on meal regulation in normal-weight human subjects. *Comm. Behav. Biol.* 6:203–8
101. Grinker, J., Strohmayer, A. J., Horowitz, J., Hirsch, J., Leibel, R. 1980. The effect of the metabolite glycerol on food intake and body weight in rats. *Brain Res. Bull.* 5: (Suppl 4):29–35
102. Hamilton, C. L. 1963. Interaction of food intake and temperature regulation in the rat. *J. Comp. Physiol. Psychol.* 56:476–88
103. Hamilton, C. L. 1967. Food and temperature. See Ref. 5, pp. 303–17
104. Hamilton, C. L. 1969. Problems of refeeding after starvation in the rat. *Ann. NY Acad. Sci.* 157 (art. 2):1004–17
105. Hamilton, C. L. 1972. Long term control of food intake in the monkey. *Physiol. Behav.* 9:1–6

106. Hammel, H. T. 1965. Neurons and temperature regulation. See Ref. 44, pp. 71–97
107. Hansen, B. C., Jen, K-L. C., Kripps, P. 1981. Regulation of food intake in monkeys: Response to caloric dilution. *Physiol. Behav.* 26:479–86
108. Harper, A. E., Boyle, P. C. 1976. Nutrients and food intake. See Ref. 30, pp. 177–206
109. Hervey, G. R. 1959. The effects of lesions in the hypothalamus in parabiotic rats. *J. Physiol.* 145:336–52
110. Hirsch, E. 1973. Some determinants of intake and patterns of feeding in the Guinea pig. *Physiol. Behav.* 11:687–704
111. Hirsch, E., Collier, G. 1974. The ecological determinants of reinforcement in the Guinea pig. *Physiol. Behav.* 12:239–49
112. Hoebel, B. G. 1969. Feeding and self-stimulation. *Ann. NY Acad. Sci.* 157 (art 2):758–78
113. Hoebel, B. G., Teitelbaum, P. 1962. Hypothalamic control of feeding and self stimulation. *Science* 135:375–77
114. Hoebel, B. G., Teitelbaum, P. 1966. Weight regulation in normal and hyperphagic rats. *J. Comp. Physiol. Psychol.* 61:189–93
115. Jacobs, H. L. 1962. Some physical, metabolic, and sensory components in the appetite for glucose. *Am. J. Physiol.* 203:1043–54
116. Janowitz, H., Grossman, M. I. 1949. Some factors affecting food intake of normal dogs and dogs with esophagostomy and gastric fistula. *Am. J. Physiol.* 159:143–48
117. Janowitz, H. D., Hollander, F. 1955. 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. Sci.* 63 (art 1):56–67
118. Jordan, H. A. 1969. Voluntary intragastric feeding: Oral and gastric contributions to food intake and hunger in man. *J. Comp. Physiol. Psychol.* 68:498–506
119. Jordan, H. A., Spiegel, T. A. 1978. Effects of simultaneous oral-gastric ingestion on meal patterns and satiety in humans. *J. Comp. Physiol. Psychol.* 92:133–47
120. Jordan, H. A., Wieland, W. F., Zebley, S. P., Stellar, E., Stunkard, A. J. 1966. Direct measurement of food intake in man: A method for objective study of eating behavior. *Psychosom. Med.* 28:836–42
121. Kanarek, R. B. 1975. Availability and caloric density of the diet as determinants of meal patterns in cats. *Physiol. Behav.* 15:611–18
122. Kanarek, R. B. 1976. Energetics of meal patterns in rats. *Physiol. Behav.* 17:395–99
123. Kanarek, R. B., Feldman, P. G., Hanes, C. 1981. Pattern of dietary self-selection in VMH lesioned rats. *Physiol. Behav.* 27:337–43
124. Kanarek, R. B., Hirsch, E. 1977. Dietary-induced overeating in experimental animals. *Fed. Proc.* 36:154–58
125. Kanarek, R. B., Marks-Kaufman, R., Lipeles, B. J. 1980. Increased carbohydrate intake as a function of insulin administration in rats. *Physiol. Behav.* 25:779–82
126. Kanarek, R. B., Ogilby, J. D., Mayer, J. 1977. Effects of dietary caloric density on feeding behavior in Mongolian gerbils. *Physiol. Behav.* 19:497–501
127. Kennedy, G. C. 1950. The hypothalamic control of food intake in rats. *Proc. R. Soc. Lond. Ser. B.* 137:535–49
128. Kennedy, G. C. 1953. The role of depot fat in the hypothalamic control of food intake in the rat. *Proc. R. Soc. Lond. Ser. B.* 140:578–92
129. Kennedy, G. C. 1973. Food intake, growth, and obesity in rats. In *Régulation de l'équilibre énergétique chez l'homme,* ed. M. Apfelbaum, pp. 1–11. Paris: Masson et Cie, Editeurs. 353 pp.
130. Kenney, N. J., McKay, L. D., Woods, S. C., Williams, R. H. 1978. Effects of intraventricular beta-endorphin on food intake of rats. *Soc. Neurosci. Abstr.* 4:176
131. Khairy, M., Morgan, T. B., Yudkin, J. 1963. Choice of diets of differing caloric density by normal and hyperphagic rats. *Brit. J. Nutr.* 17:557–68
132. Kissileff, H. R. 1968. The effects of water loading and ambient temperature changes on temporal patterns of food and water intake in the rat. Paper presented at 3rd Int. Conf. Regulation of Food and Water Intake, Haverford College, Pennsylvania, September 1968
132a. Kissileff, H. R. 1970. Free feeding in normal and recovered lateral rats monitored by a pellet-detecting eatometer. *Physiol. Behav.* 5:163–73
133. Kissileff, H. R. 1976. Consumatory behavior. In *International Encyclopedia of Psychiatry, Psychology, Psychoanalysis, & Neurology,* ed. B. Wolman, III: 352–53. NY: Human Sciences Press
134. Kissileff, H. R. 1976. Palatability. See Ref. 133, X:172
135. Kissileff, H. R., Thornton, J. 1982. Facilitation and inhibition in the cumula-

tive food intake curve in man. In *Changing Concepts of the Nervous System,* ed. A. J. Morrison, P. Strick. NY: Academic. In press

136. Kissileff, H. R., Thornton, J., Becker, E. 1982. A quadratic equation adequately describes the cumulative food intake curve in man. *Appetite* 3. In press
137. Kohn, M. 1951. Satiation of hunger from food injected directly into the stomach versus food ingested by mouth. *J. Comp. Physiol. Psychol.* 44:412–22
138. Kraly, F. S., Blass, E. M. 1976. Increased feeding in rats in a low ambient temperature. See Ref. 63, pp. 77–88
139. Kraly, F. S., Blass, E. M. 1976. Mechanisms for enhanced feeding in the cold in rats. *J. Comp. Physiol. Psychol.* 90:714–26
140. Kraly, F. S., Carty, W. J., Resnick, S., Smith, G. P. 1978. Effect of cholecystokinin on meal size and intermeal interval in the sham feeding rat. *J. Comp. Physiol. Psychol.* 92:697–707
141. Kraly, F. S., Gibbs, J. 1980. Vagotomy fails to block the satiating effect of food in the stomach. *Physiol. Behav.* 24:1007–10
142. Kraly, F. S., Smith, G. P. 1978. Combined pregastric and gastric stimulation by food is sufficient for normal meal size. *Physiol. Behav.* 21:405–8
143. Krasne, F. B. 1962. General disruption resulting from electrical stimulus of the ventromedial hypothalamus. *Science.* 138:822–23
144. Kratz, C. M., Levitsky, D. A., Lustick, S. 1978. Differential effects of quinine and sucrose-octa-acetate on food intake in the rat. *Physiol. Behav.* 20:665–67
145. KROC-Symposium. 1981. The nervous system and metabolism. *Diabetologia* 20 (suppl.)
146. Leibowitz, S. F. 1978. Paraventricular nucleus: A primary site mediating adrenergic stimulation of feeding and drinking. *Pharmacol. Biochem. Behav.* 8:163–75
147. Leibowitz, S. F. 1980. Neurochemical systems of the hypothalamus in control of feeding and drinking behavior and water-electrolyte excretion. In *Handbook of the Hypothalamus,* ed. P. J. Morgane, J. Panksepp, 3A:299–437. NY: Marcel Dekker
148. Leibowitz, S. F., Rossakis, C. 1978. Pharmacological characterization of perifornical hypothalamic β-adrenergic receptors mediating feeding inhibition in the rat. *Neuropharmacology* 17:691–702
149. Le Magnen, J. 1971. Advances in studies on the physiological control and regulation of food intake. In *Progress in Physiological Psychology,* ed. E. Stellar, J. M. Sprague, 4:203–61. NY: Academic. 363 pp.
150. Le Magnen, J. 1977. Hunger and food palatability in the control of feeding behavior. See Ref. 31, pp. 263–79
151. Le Magnen, J. 1981. The metabolic basis of the dual periodicity of feeding in rats. *Behav. Brain Sci.* 4:561–607
152. Le Magnen, J., Devos, M. 1980. Parameters of the meal pattern in rats: Their assignment and physiological significance. *Neurosci. Biobehav. Rev.* 4: (Suppl 1): 1–11
153. Le Magnen, J., Devos, M. 1980. Variations of meal-to-meal liver glycogen in rats. *Neurosci. Biobehav. Rev.* 4: (Suppl. 1) 29–32
154. Le Magnen, J., Devos, M. Gaudillière, J., Louis-Sylvestre, J., Tallon, S. 1973. Role of a lipostatic mechanism in regulation by feeding of energy balance in rats. *J. Comp. Physiol. Psychol.* 84:1–23
155. Le Magnen, J., Tallon, S. 1963. Enregistrement et analyse préliminaire de la "périodicité alimentaire spontanée" chez le rat blanc. *J. Physiol. (Paris)* 55:286–87
156. Le Magnen, J., Tallon, S. 1966. La periodicite spontanee de la prise d'aliments ad libitum du rat blanc. *J. Physiol. (Paris)* 58:323–49
157. Le Magnen, J., Tallon, S. 1968. L'effet du jeûne préalable sur les caractéristiques temporelles de la prise d'aliments chez le rat. *J. Physiol. (Paris)* 60:143–54
158. Levitsky, D. A. 1970. Feeding patterns of rats in response to fasts and changes in environmental conditions. *Physiol. Behav.* 5:291–300
159. Levitsky, D. A., Collier, G. 1968. Effects of diet and deprivation on meal eating behavior in rats. *Physiol. Behav.* 3:137–40
160. Levitsky, D. A., Faust, I. M., Glassman, M. 1976. The ingestion of food and the recovery of body weight following fasting in the naive rat. *Physiol. Behav.* 17:575–80
161. Liu, C. M., Yin, T. H. 1974. Caloric compensation to gastric loads in rats with hypothalamic hyperphagia. *Physiol. Behav.* 13:231–38
162. Louis-Sylvestre, J. 1981. Hepatic glucoreceptors do exist but do not control food intake. *Appetite* 2:146–48
163. Mackay, E. M., Calloway, J. W., Barnes, R. H. 1940. Hyperalimentation

in normal animals produced by protamine zinc insulin. *J. Nutr.* 20:59–66
164. MacLagan, N. F. 1937. The role of appetite in the control of body weight. *J. Physiol.* 90:385–94
165. Maddison, S. 1977. Intraperitoneal and intracranial cholecystokinin depress operant responding for food. *Physiol. Behav.* 19:819–24
166. Margules, D. L. 1981. Endorphinergic and endoloxonergic states of the diffuse neuroendocrine system in energy balance. See Ref. 45, pp. 361–68
167. Margules, D. L., Moisset, B., Lewis, M., Shibuya, H., Pert, P. B. 1978. β-Endorphin is associated with overeating in genetically obese mice (ob/ob) and rats (fa/fa). *Science* 202:988–91
168. Margules, D. L., Olds, J. 1962. Identical "feeding" and "rewarding" systems in the lateral hypothalamus of rats. *Science* 135:374–75
169. Marler, P., Hamilton, W. J. III. 1966. *Mechanisms of Animal Behavior.* NY: Wiley
170. Marshall, J. F., Teitelbaum, P. 1973. A comparison of the eating in response to hypothermic and glucoprivic challenges after nigral 6-hydroxydopamine and lateral hypothalamic electrolytic lesions in rats. *Brain Res.* 55:229–33
171. Martinez, I., Racotta, R., Russek, M. 1974. Hepatic chromaffin cells. *Life Sci.* 15:267–71
172. Mayer, J. 1955. Regulation of energy intake and the body weight. The glucostatic theory and the lipostatic hypothesis. *Ann. NY Acad. Sci.* 63 (art. 1): 15–43
173. Mayer, J., Marshall, N. B., Vitale, J. J., Christensen, M. B., Mashayekki, M. B., Stare, F. J. 1954. Exercise, food intake and body weight in normal rats, and genetically obese adult mice. *Am. J. Physiol.* 177:544–48
174. McCleery, R. H. 1977. On satiation curves. *Anim. Behav.* 25:1005–15
175. McHugh, P. R. 1979. Aspects of the control of feeding: Application of quantitation in psychobiology. *Johns Hopkins Med. J.* 144:147–55
176. McHugh, P. R., Moran, T. H. 1978. Accuracy of the regulation of caloric ingestion in the rhesus monkey. *Am. J. Physiol.* 235:R29–34
177. McHugh, P. R., Moran, T. H. 1979. Calories and gastric emptying: a regulatory capacity with implications for feeding. *Am. J. Physiol.* 236: R254–60
177a. McHugh, P. R., Moran, T. H., Barton, G. N. 1975. Satiety: A graded behavioral phenomenon regulating caloric intake. *Science* 190:167–69
178. Mellinkoff, S. M., Frankland, M., Boyle, D., Greipel, M. 1956. Relationship between serum amino acid concentration and fluctuations in appetite. *J. Appl. Physiol.* 8:535–38
179. Mickelsen, O., Takahashi, S., Craig, C. 1955. Experimental obesity I. Production of obesity in rats by feeding high-fat diets. *J. Nutr.* 57:541–54
180. Miller, N. E. 1955. Effects of drugs on motivation: The value of using a variety of measures. *Ann. NY Acad. Sci.* 65:318–33
181. Miller, N. E. 1960. Motivational effects of brain stimulation and drugs. *Fed. Proc.* 19:846–53
182. Mogenson, G. J., Calaresu, F. R. 1978. Food intake considered from the viewpoint of systems analysis. See Ref. 33, pp. 1–24
183. Montgomery, M. J., Baumgardt, B. R. 1965. Regulation of food intake in ruminants 2. Rations varying in energy concentration and physical form. *J. Dairy Sci.* 48:1623–28
184. Mook, D. G., Cseh, C. L. 1981. Release of feeding by the sweet taste in rats: the influence of body weight. *Appetite* 2:15–34
185. Moran, T. H., McHugh, P. R. 1981. Distinctions among three sugars in their effects on gastric emptying and satiety. *Am. J. Physiol.* 241:R25–30
186. Morley, J. E., Levine, A. S. 1980. Stress-induced eating is mediated through endogenous opiates. *Science* 209:1259–60
187. Mufson, E. J., Sclafani, A., Aravich, P. F. 1980. Fiber degeneration associated with hyperphagia-inducing knife cuts in the hypothalamus. *Exp. Neurol.* 67:633–45
188. Myers, R. D., McCaleb, M. L. 1980. Feeding: Satiety signal from intestine triggers brain's noradrenergic mechanism. *Science* 209:1035–37
189. Nicolaidis, S. 1969. Early systemic responses to orogastric stimulation in the regulation of food and water balance: functional and electrophysiological data. *Ann. NY Acad. Sci.* 157:1176–200
190. Nicolaidis, S. 1978. Role des réflexes anticipateurs oro-végétatifs dans la régulation hydrominerale et énergétique. *J. Physiol. (Paris)* 74:1–19
191. Nicolaidis, S., Rowland, N. 1976. Metering of intravenous versus oral nutrients and regulation of energy balance. *Am. J. Physiol.* 231:661–68

192. Nikoletseas, M. M. 1978. Effects of forced exercise on the food intake of rats maintained on a 23-h deprivation schedule. *Physiol. Behav.* 20:735–38
193. Nikoletseas, M. M. 1980. Food intake in the exercising rat: A brief review. *Neurosci. Biobehav. Rev.* 4:265–67
194. Novin, D. 1976. Visceral mechanisms in the control of food intake. See Ref. 63, pp. 357–67
195. Novin, D., Oomura, Y., eds. 1980. Integration of central and peripheral receptors in hunger and energy metabolism. *Brain Res. Bull.* 5 (Suppl. 4).
196. Novin, D., Sanderson, J. D., VanderWeele, D. A. 1974. The effect of isotonic glucose on eating as a function of feeding condition and infusion site. *Physiol. Behav.* 13:3–7
197. Novin, D., VanderWeele, D. A. 1977. Visceral involvement in feeding: there is more to regulation than the hypothalamus. In *Progress in Psychobiology and Physiological Psychology,* ed. J. M. Sprague, A. N. Epstein, 7:193–241. NY: Academic. 257 pp.
198. Oomura, Y., Kita, H. 1981. Insulin acting as a modulator of feeding through the hypothalamus. *Diabetologia* 20: (Suppl.) 290–98
199. Oscai, L. B., Mole, P. A., Holloszy, J. O. 1971. Effects of exercise on cardiac weight and mitochondria in male and female rats. *Am. J. Physiol.* 220: 1944–48
200. Ostrowski, N. L., Foley, T., Lind, M. D., Reid, L. D. 1980. Naloxone reduces fluid intake: effects of water and food deprivation. *Pharmacol. Biochem. Behav.* 12:431–35
201. Overmann, S. R. 1976. Dietary self-selection by animals. *Psychol. Bull.* 83:218–35
202. Panksepp, J. 1971. Effects of fats, proteins, and carbohydrates on food intake in rats. *Psychonomic Monog. Suppl.* 4:85–95
203. Panksepp, J. 1974. Hypothalamic regulation energy balance and feeding behavior. *Fed. Proc.* 33:1150–65
204. Panksepp, J., Meeker, R. 1977. Effects of insulin and hypothalamic lesions on glucose preference in rats. See Ref. 31, pp. 343–56
205. Panksepp, J., Nance, D. M. 1972. Insulin, glucose, and hypothalamic regulation of feeding. *Physiol. Behav.* 9:447–51
206. Parameswaran, S. V., Steffens, A. B., Hervey, G. R., de Ruiter, L. 1977. Involvent of a humoral factor in the regulation of body weight in parabiotic rats. *Am. J. Physiol.* 232:R150–57
207. Parizkova, J., Pupa, O. 1963. Some metabolic consequences of adaptation to muscular work. *Brit. J. Nutr.* 17: 341–45
208. Peck, J. W. 1978. Rats defend different body weights depending on palatability and accessibility of their food. *J. Comp. Physiol. Psychol.* 92:555–70
209. Penicaud, L., Le Magnen, J. 1980. Recovery of body weight following starvation or food restriction in rats. *Neurosci. Biobehav. Res.* 4:47–52
210. Peters, J. C., Harper, A. E. 1981. Protein and energy consumption, plasma amino acid ratios, and brain neurotransmitter concentrations. *Physio. Behav.* 27:287–98
211. Porikos, K. 1981. Control of food intake in man: Response to covert caloric dilution of a conventional and palatable diet. See Ref. 45, pp. 83–87
212. Porikos, K. P., Booth, G., Van Itallie, T. B. 1977. Effect of covert nutritive dilution on the spontaneous food intake of obese individuals: a pilot study. *Am. J. Clin. Nutr.* 30:1638–44
213. Porte, D., Woods, S. C. 1981. Regulation of food intake and body weight by insulin. *Diabetologia.* 20: (Suppl.) 274–80
214. Powley, T. L. 1977. The ventromedial hypothalamic syndrome, satiety, and a cephalic phase hypothesis. *Psychol. Rev.* 84:89–126
215. Quartermain, D., Kissileff, H. R., Shapiro, R., Miller, N. E. 1971. Suppression of food intake with intragastric loading: Relation to natural feeding cycle. *Science* 173:941–43
216. Racotta, R., Vega, C., Russek, M. 1972. Liver catecholamines and preabsorptive satiation. *Fed. Proc.* 31:309 (Abstr.)
217. Richter, C. P. 1927. Animal behavior and internal drives. *Q. Rev. Biol.* 2:307–43
218. Richter, C. P., Holt, L. E., Barelare, B. 1938. Nutritional requirements for normal growth and reproduction in rats studied by the self-selection method. *Am. J. Physiol.* 122:734–44
219. Richter, C. P., Schmidt, E. C. H. 1941. Increased fat and decreased carbohydrate appetite in pancreatectomized rats. *Endocrinology* 28:179–92
220. Ritter, R. C., Epstein, A. N. 1975. Control of meal size by central noradrenergic action. *Proc. Natl. Acad. Sci.* 72:3740–43
221. Ritter, R. C., Roelke, M., Neville, M. 1978. Glucoprivic feeding behavior in

absence of other signs of glucoprivation. *Am. J. Physiol.* 234:E617–21
222. Ritter, R. C., Slusser, P. 1980. 5-Thio-D-glucose causes increased feeding and hy rglycemia in the rat. *Am. J. Physiol.* E141–44
223. Ritter, R. C., Slusser, P., Stone, S. 1981. Glucoreceptors controlling feeding and blood glucose: Location in the hindbrain. *Science* 213:451–53
224. Rolls, B. J. 1981. Palatability and food preference. See Ref. 45, pp. 271–78
225. Rolls, B. J., Rolls, E. T., Rowe, E. A., Sweeney, K. 1981. Sensory specific satiety in man. *Physiol. Behav.* 27:137–42
226. Rolls, B. J., Rowe, E. A., Rolls, E. T., Kingston, B., Megson, A., Gunary, R. 1981. Variety in a meal enhances food intake in man. *Physiol. Behav.* 26: 215–21
227. Rolls, B. J., Rowe, E. A., Turner, R. C. 1980. Persistent obesity in rats following a period of consumption of a mixed high energy diet. *J. Physiol.* 298:415–27
228. Rolls, E. T. 1976. Neurophysiology of feeding. See Ref. 30, pp. 21–42
229. Rothwell, N. J., Stock, M. J. 1978. A paradox in the control of energy intake in the rat. *Nature* 273:146–47
230. Rothwell, N. J., Stock, M. J. 1979. Regulation of energy balance in the rat. *J. Comp. Physiol. Psychol.* 93:1024–34
231. Rothwell, N. J., Stock, M. J. 1979. A role for brown adipose tissue in diet-induced thermogenesis. *Nature* 281:31–35
232. Routtenberg, A. 1968. "Self-starvation" of rats living in activity wheels: adaptation effects. *J. Comp. Physiol. Psychol.* 66:234–38
233. Routtenberg, A., Kuznesof, A. W. 1967. "Self-starvation" of rats living in activity wheels on a restricted [redacted] schedule. *J. Comp. Physiol.* 64:414–21
234. Rowland, N., Stricker, E. M. 1979. Differential effects of glucose and fructose infusions on insulin induced feeding in rats. *Physiol. Behav.* 22:387–89
235. Rozin, P. 1968. Are carbohydrate and protein intakes separately regulated: *J. Comp. Physiol. Psychol.* 65:23–29
236. Russek, M. 1963. An hypothesis on the participation of hepatic glucoreceptors in the control of food intake. *Nature* 197:79–80
237. Russek, M. 1981. Current status of the hepatostatic theory of food intake control. *Appetite* 2:137–43
238. Russek, M. 1981. Reply to commentary on "Current status of the hepatostatic theory of food intake control." *Appetite* 2:157–62
239. Russek, M., Grinstein, S. 1974. Coding of metabolic information by hepatic glucoreceptors. In *Neurohumoral Coding of Brain Function,* ed. R. D. Myers, R. R. Drucker-Colin, pp. 81–97. NY: Plenum
240. Russek, M., Rodriguez-Zenejas, A. M., Piña, S. 1968. Hypothetical liver receptors and the anorexia caused by adrenaline and glucose. *Physiol. Behav.* 3:249–57
241. Samanin, R., Garattini, S., eds. 1978. *Central Mechanisms of Anorectic Drugs.* NY: Raven Press
242. Sawchenko, P. E., Gold, R. M. 1981. Effects of gastric vs complete subdiaphragmatic vagotomy on hypothalamic hyperphagia and obesity. *Physiol. Behav.* 26:281–92
243. Sawchenko, P. E., Gold, R. M., Alexander, J. 1981. Effects of selective vagotomies on knife cut–induced hypothalamic obesity: differential results on lab chow vs high-fat diets. *Physiol. Behav.* 26:293–300
244. Schemmel, R., Mickelsen, O., Gill, J. L. 1970. Dietary obesity in rats: body weight and body fat accretion in seven strains of rat. *J. Nutr.* 100:1941–48
245. Schwartzbaum, J. S., Ward, H. P. 1958. An osmotic factor in the regulation of food intake in the rat. *J. Comp. Physiol. Psychol.* 51:555–60
246. Sclafani, A. 1976. Appetite and hunger in experimental obesity syndromes. See Ref. 63, pp. 281–95
247. Sclafani, A. 1981. The role of hyperinsulinemia and the vagus nerve in hypothalamic hyperphagia reexamined. *Diabetologia* 20:(Suppl.)402–10
248. Sclafani, A., Aravich, P. F., Landman, M. 1981. Vagotomy blocks hypothalamic hyperphagia in rats on a chow diet and sucrose solution, but not on a palatable mixed diet. *J. Comp. Physiol. Psychol.* 95:720–34
249. Sclafani, A., Berner, C. N. 1976. Influence of diet palatability on meal taking behavior of hypothalamic hyperphagic and normal rats. *Physiol. Behav.* 16:355–63
250. Sclafani, A., Gorman, A. N. 1977. Effects of age, sex, and prior body weight on the development of dietary obesity in adult rats. *Physiol. Behav.* 18:1021–26
251. Share, I., Martyniuk, E., Grossman, M. I. 1952. Effect of [redacted] intragastric feeding on oral f[redacted]n dogs. *Am. J. Physiol.* 169:229–35

252. Sharma, K. N., Dua-Sharma, S., Jacobs, H. L. 1975. Electrophysiological monitoring of multilevel signals related to food intake. See Ref. 79, pp. 194–212
253. Silverman, H. J., Zucker, I. 1976. Absence of post-fast food compensation in the golden hamster. *Physiol. Behav.* 17:271–85
254. Skinner, B. F. 1932. Drive and reflex strength. *J. Gen. Psychol.* 6:22–47
255. Skinner, B. F. 1936. Conditioning and extinction and their relation to drive. *J. Gen. Psychol.* 14:296–317
256. Slusser, P. G., Ritter, R. C. 1980. Increased feeding and hyperglycemia elicited by intracerebroventricular 5-thioglucose. *Brain Res.* 202:474–78
257. Smith, G. P., Epstein, A. N. 1969. Increased feeding in response to decreased glucose utilization in the rat and monkey. *Am. J. Physiol.* 217:1083–87
258. Smith, G. P., Gibbs, J. 1979. Postprandial satiety. See Ref. 197, pp. 179–242
259. Smith, G. P., Gibbs, J. 1981. Brain gut peptides and the control of food intake. In *Neurosecretion and Brain Peptides,* ed. J. B. Martin, S. Reichlin, K. L. Bick, pp. 389–95. NY: Raven Press
260. Smith, G. P., Jerome, C., Cushin, G. J., Eterno, R., Simansky, K. J. 1981. Abdominal vagotomy blocks the satiety effects of cholecystokinin in the rat. *Science* 213:1036–37
261. Smith, G. P., Gibbs, J., Jerome, C., Pi-Sunyer, F. X., Kissileff, H. R., Thornton, J. 1982. The satiety effect of cholecystokinin: A progress report. *Pharmacol. Biochem. Behav.* In press
262. Smith, M. H. Jr. 1966. Effect of hypertonic preloads on concurrent eating and drinking. *J. Comp. Physiol. Psychol.* 61:398–401
262a. Smith, M., Duffy, M. 1955. The effects of intragastric inejection of various substances on subsequent bar-pressing. *J. Comp. Physiol. Psychol.* 48:387–91
263. Smith, M., Duffy, M. 1957. Some physiological factors that regulate eating behavior. *J. Comp. Physiol. Psychol.* 50:601–8
264. Smith, M., Pool, R., Weinberg, H. 1959. The effect of peripherally induced shifts in water balance on eating. *J. Comp. Physiol. Psychol.* 52:289–93
265. Smith, M., Pool, R., Weinberg, H. 1962. The role of bulk in the control of eating. *J. Comp. Physiol. Psychol.* 55: 115–20
265a. Smutz, E. R., Hirsch, E., Jacobs, H. L. 1975. Caloric compensation in hypothalamic obese rats. *Physiol. Behav.* 14:305–9
266. Snowdon, C. T. 1969. Motivation, regulation and the control of meal patterns with oral and intragastric feeding. *J. Comp. Physiol. Psychol.* 69:91–100
267. Snowdon, C. T. 1970. Gastrointestinal sensory and motor control of food intake. *J. Comp. Physiol. Psychol.* 71:68–76
268. Snowdon, C. T. 1975. Production of satiety with small intraduodenal infusions in the rat. *J. Comp. Physiol. Psychol.* 88:231–38
269. Spiegel, T. A. 1973. Caloric regulation of food intake in man. *J. Comp. Physiol. Psychol.* 84:24–37
270. Spitzer, L., Rodin, J. 1981. Studies of human eating behavior: A critical review of normal weight and overweight individuals. *Appetite* 2:293–330
271. Stapelton, J. M., Merriman, V. J., Coogle, C. L., Gelbard, S. D., Reid, L. D. 1979. Naloxone reduces pressing for intracranial stimulation of sites in the periaqueductal gray area, accumbens nucleus, substantia nigra, and lateral hypothalamus. *Physiol. Psychol.* 7: 427–36
272. Steffens, A. B. 1975. Influence of reversible obesity on eating behavior, blood glucose, and insulin in the rat. *Am. J. Physiol.* 228:1738–44
273. Stellar, E. 1960. Drive and motivation. In *Handbook of Physiology, Sect. I, Neurophysiology,* ed. H. W. Magoun, 3:1501–27. Washington DC: Am. Physiol. Soc.
274. Stevenson, J. A. F., Box, B. M., Feleki, U., Beaton, J. R. 1966. Bouts of exercise and food intake in the rat. *J. Appl. Physiol.* 21:118–22
275. Stricker, E. M., Rowland, N. 1978. Hepatic versus cerebral origin of stimulus for feeding induced by 2-Deoxy-d-glucose in rats. *J. Comp. Physiol. Psychol.* 92:126–32
276. Stricker, E. M., Rowland, N., Saller, C. F., Friedman, M. I. 1977. Homeostasis during hypoglycemia: central control of adrenal secretion and peripheral control of feeding. *Science* 196:79–81
277. Strominger, J. L., Brobeck, J. R., Cort, R. L. 1953. Regulation of food intake in normal rats and rats with hypothalamic hyperphagia. *Yale J. Biol. Med.* 26:55–74
278. Stunkard, A. J., ed. 1980. *Obesity.* Philadelphia: W. B. Saunders, Co.
279. Sullivan, A. C., Triscari, J., Conai, K. 1978. Caloric compensatory responses to diets containing either nonabsorbable

carbohydrate or lipid by obese and lean Zucker rats. *Am. J. Clin. Nutr.* 31:S261–66

280. Teghtsoonian, M., Becker, E., Edelman, B. 1981. A psychophysical analysis of perceived satiety: its relation to consummatory behavior and degree of overweight. *Appetite* 2:217–29
281. Teitelbaum, P. 1955. Sensory control of hypothalamic hyperphagia. *J. Comp. Physiol. Psychol.* 48:158–63
282. Teitelbaum, P. 1966. The use of operant methods in the assessment and control of motivational states. In *Operant Behavior: Areas of Research and Application,* ed. W. K. Honig, pp. 565–608. NY: Meredith Publ. Co.
283. Teitelbaum, P. 1967. Motivation and control of food intake. See Ref. 5, pp. 319–35
284. Teitelbaum, P., Campbell, B. A. 1958. Ingestion patterns in normal and hyperphagic rats. *J. Comp. Physiol. Psychol.* 51:135–41
285. Thomas, D. W., Mayer, J. 1968. Meal taking and regulation of food intake by normal and hypothalamic hyperphagic rats. *J. Comp. Physiol. Psychol.* 66:642–53
286. Thompson, D. A., Campbell, R. G. 1977. Hunger in humans induced by 2-Deoxy-D-glucose: Glucoprivic control of taste preference and food intake. *Science.* 198:1065–1067.
287. Toates, F. M. 1978. A physiological control theory of the hunger-thirst interaction. See Ref. 33, pp. 347–73
288. Toates, F. M. 1981. The control of ingestive behavior by internal and external stimuli—a theoretical review. *Appetite* 2:35–50
289. VanderWeele, D. A., Geiselman, P. J., Novin, D. 1979. Pancreatic glucagon, food deprivation and feeding in intact and vagotomized rabbits. *Physiol. Behav.* 23:155–58
290. VanderWeele, D. A., Haraczkiewicz, E., Di Conti, M. 1980. Pancreatic glucagon administration, feeding, glycemia and liver glycogen in rats. *Brain Res. Bull.* 5: (Suppl. 4) 17–21
291. VanderWeele, D. A., Novin, D., Rezek, M., Sanderson, J. D. 1974. Duodenal or hepatic-portal glucose perfusion: Evidence for duodenally-based satiety. *Physiol. Behav.* 12:467–73
292. VanderWeele, D. A., Sanderson, J. D. 1976. Peripheral glucosensitive satiety in the rabbit and the rat. See Ref. 33, pp. 383–93
293. VanderWeele, D. A., Skoog, D. R., Novin, D. 1976. Glycogen levels and peripheral mechanism of glucose-induced suppression of feeding. *Am. J. Physiol.* 231:1655–59
294. Van Hemel, S. B., Myer, J. S. 1969. Feeding patterns and response to caloric dilution in the Japanese quail. *Physiol. Behav.* 4:339–44
295. Van Itallie, T. B., Gale, S. K., Kissileff, H. R. 1978. Control of food intake in the regulation of depot fat: an overview. In *Advances in Modern Nutrition,* vol. 2. *Diabetes, Obesity, and Vascular Disease Metabolic and Molecular Interrelationships,* Part 2, ed. H. M. Katzen, R. J. Mahler, pp. 427–92. Washington DC: Hemisphere Publ. Corp.
296. Van Itallie, T. B., VanderWeele, D. A. 1981. The phenomenon of satiety. In *Recent Advances in Obesity Research: III,* ed. P. Bjorntorp, M. Cairella, A. N. Howard, pp. 278–89. London: John Libbey. 392 pp.
297. Vilberg, T. R., Beatty, W. W. 1975. Behavioral changes following VMH lesions in rats with controlled insulin levels. *Pharmacol. Biochem. Behav.* 3: 377–84
298. Wagner, J. W., De Groot, J. 1963. Changes in feeding behavior after intracerebral injections in the rat. *Am. J. Physiol.* 204:483–87
299. Waldbillig, R. J., Bartness, T. J., Stanley, B. G. 1981. Increased food intake, body weight and adiposity, in rats after regional neurochemical depletion of serotonin. *J. Comp. Physiol. Psychol.* 95:391–405
300. Walike, B. C., Jordan, H. A., Stellar, E. 1969. Preloading and the regulation of food intake in man. *J. Comp. Physiol. Psychol.* 68:327–33
301. Wirtshafter, D., Davis, J. D. 1977. Body weight: Reduction by long-term glycerol treatment. *Science* 198: 1271–74
302. Wirtshafter, D., Davis, J. D. 1977. Set points, settling points, and the control of body weight. *Physiol. Behav.* 19:75–78
303. Wolff, F. W., Bartoshuk, L. M., Booth, D. A., Bray, G. A., Chlouverakis, C. S., Curtis-Prior, P. B., Harper, A. E., Hunt, J. N., Novin, D., Russek, M. B., Schneider, K., Smith, G. P. 1976. Peripheral and hormonal mechanisms—group report 2. See Ref. 30, pp. 219–28

303a. Woo, R. 1981. *Effect of exercise on spontaneous caloric intake in obesity.* PhD thesis, Columbia Univ., New York. 194 pp.

304. Woo, R., Garrow, J., Pi-Sunyer, F. X. 1982. Voluntary food intake during pro-

longed exercise in obese women. *Am. J. Clin. Nutr.* In press
305. Woo, R., Kissileff, H. R., Pi-Sunyer, F. X. 1979. Is insulin a satiety hormone? *Fed Proc.* 38:547 (Abstr.)
306. Woods, S. C., Lotter, E. C., McKay, L. D., Porte, D. 1979. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* 282:503–5
307. Woods, S. C., Porte, D. Jr. 1977. Relationship between plasma and cerebrospinal fluid insulin levels of dogs. *Am. J. Physiol.* 233:E331–34
308. Woods, S. C., West, D. B., Stein, L. J., McKay, L. D., Lotter, E. C., Porte, S. G., Kenney, N. J., Porte, D. Jr. 1981. Peptides and the control of meal size. *Diabetologia.* 20: (Suppl.) 305–13
309. Wooley, O. W. 1971. Long-term food regulation in the obese and nonobese. *Psychosom. Med.* 33:436–44
310. Wurtman, J. J., Wurtman, R. J. 1979. Drugs that enhance serotonergic transmission diminish elective carbohydrate consumption by rats. *Life Sci.* 24:895–904
311. Yin, T. H., Hamilton, C. L., Brobeck, J. R. 1970. Food intake of rats given hypertonic solutions by gavage and water intravenously. *Proc. Soc. Exp. Biol. Med.* 133:83–85
312. Young, P. T. 1967. Palatability: the hedonic response to foodstuffs. See Ref. 5, pp. 353–66
313. Young, T. K., Liu, A. C. 1965. Hyperphagia, insulin and obesity. *Chin. J. Physiol.* 19:247–53
314. Ziegler, H. P., Green, H. L., Siegel, S. 1972. Food and water intake and weight regulation in the pigeon. *Physiol. Behav.* 8:127–34