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Control System for Hunger and its Implications in Animals and Man

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METABOLIC INFLUENCE ON HUNGER

The current multifactor approach to the explanation of hunger includes a role for influences of bodily metabolism. The most widely favored idea appears to be that metabolism of glucose in a specialized part of the central or peripheral nervous system produces short-term inhibitory effects, and some representation of adipose triglyceride stores produces adjustments in food intake which promote the long-term precision of energy regulation.

These metabolic hunger signals are unlikely to be identified without techniques to separate normal metabolic influences on feeding from confounding nonmetabolic effects. The remarkable fact is that, in the 20 years of the glucostatic and lipostatic theories, there has been no proof that metabolism of ingested food affects hunger at all, let alone an experimental paradigm in which metabolic factors could be studied in isolation.

Postabsorptive Satiation

The first such proof and paradigm was reported in Cambridge in 1971 (Fourth International Conference on the Regulation of Food and Water Intake; see Introduction in ref. 1) and is at last due to be published in full (2). It depends on the very simple maneuver of waiting for all the ingested food to be absorbed in an otherwise little-deprived rat and then testing for a residual inhibitory effect on feeding. Under conditions of fast absorption (by night in the rat), hunger is lessened for 1 hr or more after all the original load has passed from the stomach and intestine. The effect does not depend on the nutrient having passed the mouth, nor on the release of intestinal hormones during absorption. The strength of the effect appears to relate to the speed with which an absorbed nutrient is used for energy by the liver—fructose given intraportally being more effective than glucose, and galactose being ineffective.

In retrospect, it is unfortunate that experimenters have generally used starved animals, hypertonic hydrolyzed nutrients, unnatural routes and rates

of administration, and the drastic metabolic insults resulting from large doses of insulin or 2-deoxyglucose. An insistence on arbitrary criteria of good experimental control—large effects, small variance—has only served to obscure the important phenomena. If what matters is the normal satiating effect of food, then one will use animals that are at most mildly deprived, administer chow or its major components (i.e., starch, with some protein), and expect changes in food intake similar in size to the imposed variation in nutrient input. A proportionately small, fairly variable effect will then (if statistically reliable) have some chance of being relevant to normal hunger control.

Ventromedial Hypothalamus is Not the Metabolic Satiety Center

One application of the postabsorptive satiation paradigm to scientific problems of obesity would be to test the hypothesis that metabolic influences on feeding act via receptors in the ventromedial hypothalamus (VMH). If that were so, the rat with bilateral VMH lesions should fail to suppress food intake following complete absorption of a nutrient load.

The notion that the VMH is the satiety center has recently been strongly challenged on a number of grounds (3–5). Nevertheless, such an experiment is crucial because the existing literature fails to show whether or not tissue in the VMH is important in the inhibition of feeding specifically by metabolism. Earlier experiments in which VMH rats show no deficit did not look at normal metabolic influences on hunger, but either at the colligative effects of concentrated solutions in the gut or at the cellular glucopenic stimulus, which is thought not to have a role in normal feeding. Abnormalities in responses to nutrients have been reported but they are attributable to taste hypersensitivity (6), to overreactivity (7) during stress induced by intraperitoneal glucose (8), or to hormonal deficits crucial under extended deprivation (4).

The postabsorptive satiety effect of a meal-sized load of chow or starch in intact rats was suitably small—approximately the size of the load (Table 1). Rats with ventromedial lesions showed normal suppression of food intake following absorption. These were bilateral anodal lesions (0.5 to 1.1 mA, 15 to 30 sec) which completely destroyed the VMH nuclei and generally damaged tissue laterally and dorsally out to the fornix and ventrally to the base of the brain. Rats with similar size lesions dorsal and lateral to the fornix showed satiety deficits. The extensive anterior elaboration of this critical area will be reported in detail elsewhere. If there are diencephalic metabolic receptors controlling feeding, they may be perifornical, like the tissue mediating endocrine responses to cellular glucopenia (9).

Postabsorptive Satiety in Man

We are much further from proving the existence of metabolic satiation in man, but we do have a satiety effect which is harder than most to attribute to

TABLE 1. *Inhibition of food intake following absorption of loads*

Group	Body weight gain (g)	Mean food intake in 2 hr test				Satiety effect					
		after nothing (g)	after saccharin (g)	after 1 g starch (g)	after 2 g chow (g)	nothing minus starch		saccharin minus starch		nothing minus chow	
						SEM	*p*	SEM	*p*	SEM	*p*
Intact	57	7.71	7.93	6.52	6.21	0.32	0.01	0.28	0.001	0.64	0.1
Ventromedial lesion	178	6.48	6.62	5.55	4.58	0.12	0.001	0.26	0.01	0.14	0.001
Dorsolateral lesion	51	6.45	6.36	6.46	6.51	0.09	$>0.1^{a,b}$	0.07	$>0.1^{a}$	0.22	$>0.1^{b}$

Maintenance chow powder was removed for 5 hr in the dark phase. Loads taken voluntarily 2 hr before refeeding, leaving time for complete absorption (2). There were four male and four female rats in each group. No dorsolateral rat had been aphagic. Satiety effect differs from that in [a]intact group and [b]ventromedial group by Mann-Whitney U test ($p < 0.05$).

p-values, mean difference from zero by correlated *t* test.

preabsorptive mechanisms. It too correlates with rapid absorption of ready energy.

In 1970, we reported that the 50-g load of glucose typically given in glucose tolerance tests had a suppressant effect on food intake in man not dependent on its sweet taste (10). Shortly after that work, we found that the same amount of starch, which has negligible osmotic effects in the lumen of the gastrointestinal tract, had indistinguishable suppressant effects on intake of ordinary foods in undeprived human subjects. The maximum effect was also delayed by 10 to 20 min in many subjects. When the concentrated starch load was given by stomach tube to remove mediation by taste, blood glucose concentration started to rise within 5 min of intubation. The rise over the first 20 min was so fast that it overtook the more rapidly initiated hyperglycemia resulting from a gastric load of the same amount and concentration of glucose. Most of the starch load but less of the glucose load was lost from the stomach within 10 min of loading. The same lag in digestion which delayed the onset of hyperglycemia presumably delayed the onset of appropriately strong inhibition of gastric evacuation by the action of starch-derived glucose on the duodenal osmoreceptors.

The contrast in satiating effects between starch and carboxymethylcellulose in suitably disguised concentrated loads provides a suitable manipulation for sensitivity training in people who seem insufficiently aware of postingestive satiation.

QUANTITATIVE MODEL OF METABOLIC CONTROL OF FEEDING

Once having proved that metabolism can affect feeding, we became increasingly impressed with the way intermeal intervals, the amount taken in meals, and the cumulative total intake all respond rapidly to suitably moderate imposed variations in energy input of any sort (1, 11). Even the less direct influences of conditioning or learning on the control of food intake were strikingly dependent on effects that seemed likely to be metabolic (12–14).

At times, multifactor theorizing seemed to be little more than the trivial assertion that feeding can be affected by almost anything. It was a tempting strategy to reject that orientation and to erect an alternative working hypothesis that the single basic controlling influence was energy supply. Russek (15) tried to explain all hunger phenomena by a hepatic glucoreceptor and many of his arguments could be transferred to an energostatic theory. The plethora of glucostats, aminostats, thermostats, and lipostats could be unified by the biochemically obvious step of invoking the Krebs cycle and cellular respiration (16). The long-standing biochemical concept that the liver uses any available energy substrate to spare the supply of glucose for the brain (and the pancreas) could point to a link between peripheral energy metabolism and central or local glucoreceptor systems. With such a control mecha-

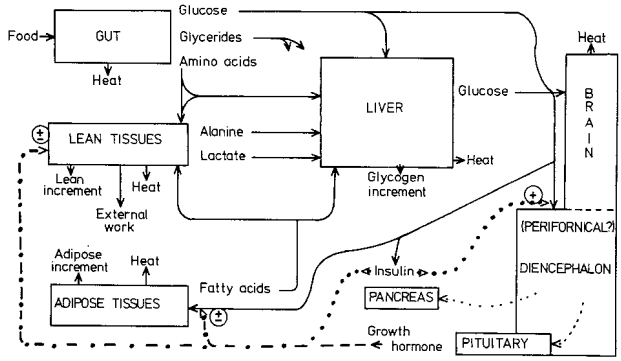

FIG. 1. Some major energy flows between tissues in the laboratory rat and their hormonal modulation.

nism, there would be no need for biochemically separate representation of fat metabolism in the brain.

A crude abstract of current views on the metabolite transfers and conversions between and within the organs of the body is given in Fig. 1. By coincidence or by confluence of thought, data have recently become available providing a bare minimum for even cruder estimates of the division of metabolizable energy supply between tissues similar to the hunger receptor and dissimilar tissues.

Absorption

By far the largest and most variable energy supply is absorption from the intestine. In the rat, this is considerably faster by night than by day (Fig. 2). The clearance function in spontaneously feeding rats appears to be similar to that more easily measured in mildly deprived and refed animals (Fig. 2, dark phase). Probably because under our conditions there is sufficient food in the duodenum to keep gastric evacuation under normal control, we do not find the inordinate rush of food to the intestine which is seen immediately after a meal in starved rats (17). Nevertheless, the stomach is emptying much faster at that stage, and so digestive enzyme secretion must be fast and anticipatory.

Our data on the clearance of glucose loads, either mixed with chow (11) or not (2; see also Fig. 2), and of chow meals (Fig. 2) are linearized better by square-root functions than by exponentials. Furthermore, when we substitute the best-fit exponential functions for the square-root gut-clearance functions in Mark 1 of our energy flow model of feeding control (18), the meal pattern predictions are wildly unrealistic, especially in the dark phase (Table 2). Hopkins (19) pointed out that a square-root relationship would be expected if the fundal-duodenal pump were controlled by a balloon-like response of the antrum to its volume of contents. However, we should not wax too meta-

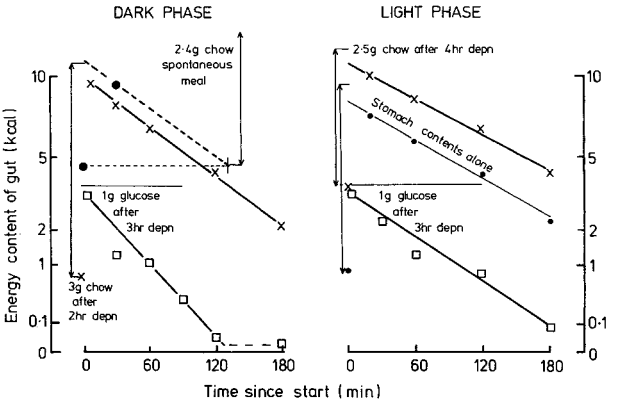

FIG. 2. Energy absorption from gut—metabolizable energy equivalent of dry weight recovered from stomach and small intestine of the rat (two to three rats per point). X, food-deprived rats permitted to consume a fixed amount of maintenance chow (vertical bar); ● (dark phase only), gut contents at start of spontaneous meal in freely fed rats, and 30 min later (clearance line by extrapolation to the mean inter-meal interval of 130 min); □, clearance of a glucose load (2). Note that gut contents are given on a square-root scale.

physical about the square-root function. In other circumstances, exponential or even linear equations might fit better.

Laboratory chow is typically half starch, one-fifth to one-quarter protein, and a very few percent triglyceride and other fats. In our initial model, to transform our glucose clearance data into estimates of chow clearance, we ignored the fat content of chow (Fig. 1) and took starch and protein to be calorically equivalent to glucose. However, not only do we have some chow clearance data but also Hunt and Stubbs (20) have argued (from a collation of data on human gastric emptying) that the characteristics of the controlling duodenal receptors are such that the stomach clears and absorption proceeds according to energy yield independently of the proportions of carbohydrate, protein, and fat. If this generalization proves sufficiently robust and precise, then we will need details of the time-course of clearance for only one representative dietary mixture.

TABLE 2. *Gut clearance function (Mark I)*

	Square root	Exponential
Light phase		
Amount eaten (g)	7.6	5.1
Number of meals	3	5
Mean meal size (g)	2.6	1.0
Dark phase		
Amount eaten (g)	13.0	12.7
Number of meals	7	22
Mean meal size (g)	1.9	0.6

Circadian Variation in Energy Storage and Expenditure

We allowed for the circadian rhythm in fat deposition and mobilization in the earlier versions of the model (18, 21). The heat production rhythm is estimated on the basis of metabolic rate values in the current version (Fig. 3). We used the 2-hr averages estimated from respiratory data for 10 rats by Le Magnen and Devos (22). Le Magnen et al. (23) give RQs and metabolic rates based on 20 rats and we now use values calculated from their Fig. 2 using the earlier equations (22); this gives a lower metabolic rate and a much less marked lipogenesis-lipolysis cycle. Note that such data serve the model as interim estimates of energy diverted away from (and fed to) the receptor system by consumption in different types of tissue. The lipid function is not total energy storage, which would include growth in lean mass. Also, metabolic rate is not used to model total energy flow between the organism and the environment.

Shorter-term variations in energy disposition will be incorporated into later versions of the model. We shall have to use respiratory data initially, although they are subject to activity artifacts under such conditions. The small change in metabolic rate around meals (22, 24), and many other types of experi-

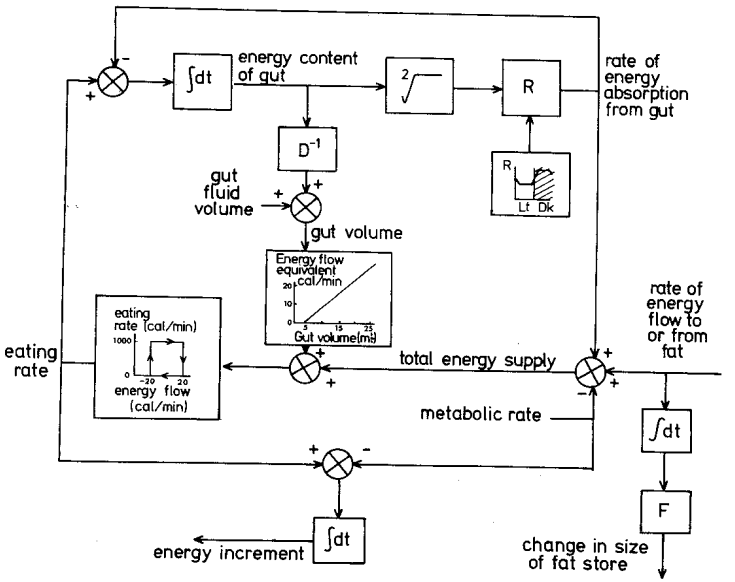

FIG. 3. Feeding model Mark 2D. The system is mathematically determinate and all functions and values are specified by physiological measurements. R, gut clearance rate constant (usually a large fraction of unity); D, energy density of food (cal/g); F, energy density of fat. The integrals are in fact programmed as successive additions, e.g., at 10-sec intervals. The model will predict temporal patterns of feeding bouts, gut contents, actual or virtual inhibition or facilitation of feeding by energy supply, change in total body energy.

ments, clearly indicate large changes in net metabolite flows into adipose tissue, liver, and muscle in parallel to absorption. Eventually it should be possible to model the control of these energy distributions at the level of interactions between absorption and hormone secretion in the way that blood glucose has been modeled.

Hunger and Satiety Thresholds

From gut clearance rates at the start and finish of meals (Fig. 2) and from hepatic portal infusion rates that just fail to prevent the release of feeding and just succeed in suppressing feeding altogether (25), we estimated absorption rates at which feeding was switched on or off in the rat with continuous access to a single familiar diet. Allowing for a metabolic rate of approximately 40 cal/min in Mark 2 (Fig. 3), the threshold values we used in Mark 1 (18, 21) become approximately −20 and +20 cal/min. This symmetry, and rounding to the decade, is well within the error limits on the absorption threshold data. As long as data do not preclude the notion, we like the idea of only one receptor system which operates with a null point of zero net energy flow and has a detection problem approximately equal for energy consumption and energy excess. The predictions of the model are not highly sensitive to the value of symmetrical thresholds in the 15 to 25 cal/min range. Asymmetry is more serious, especially for the energy increment predictions (*in preparation*).

Nearly all receptors respond to a flux of material or energy or to a partial pressure (concentration, force). The adequate stimulus to the metabolic hunger receptor may prove to be concentration of glucose at the neuronal membrane or of some metabolite within the cell, but the necessary combination of neurophysiology, biochemistry, and behavior to elucidate the matter is still some way off. Even then, the functional stimulus could still be the speed at which energy is being supplied. Engineers find proportional control very useful to add to the stability of a control system. If a flow rate is tightly coupled to the quantity held in a source (e.g., as with gut clearance in the model), control according to instantaneous flow rate will stabilize quantity in the absence of any set point for amount in the system. Our provisional commitment to a rate-sensing system was clinched by the fact that approximate estimates of the major variations in energy flow are currently practicable, whereas data on quantities of crucial metabolites or body constituents are not as readily available.

Distension at Large Gut Volumes

When we modeled the diabetic rat as having insensitive energy flow receptors (21), meals large enough to burst the stomach were predicted in the absence of inhibition from distension. Unfortunately, we cannot locate useable rat data on distension receptors, and none of the electrophysiological work is

directly related to behavior. We therefore use Paintal's (25) data on the effects of antral distension on vagal firing rate in the cat. The volumes are divided by 10, scaling down relative to body weight. Complete inhibition purely from distension is set at the physical limit of rat stomach volume (40 ml). In Mark 2 with distension (Mark 2D, Fig. 3), this inhibition is calculated as a virtual energy flow. It could be a real energy flow if distension inhibits via a glycogenolytic reflex (15). Gut volume is calculated by multiplying the energy content of the gut by the reciprocal of the energy density of food and adding an equal volume of fluid, which is what drinking, salivation, and gastrointestinal secretion are attuned to do (27).

Eating Rate

We model the food energy input rate as either zero or constant. Under some conditions, eating rate at the beginning of a meal shows a transient acceleration as a joint function of dietary palatability and duration of prior food deprivation. This has been interpreted as reflecting a positive feedback mechanism, serving to lock the animal into persistent feeding activity. Also, it is widely supposed that ingestion rate steadily goes down toward the end of a bout, although this impression may largely be an artifact of grouping data from animals or occasions when bouts at nearly constant rate end at different times. In our experience of rats with continuous access to chow a mouthful at a time (28, 29), these accelerative and decelerative phases are relatively short and often undetectable. Immediately graspable pellets of normal palatability are taken at approximately 300 mg/min, which (at an energy density of 3.4 kcal/g) gives the modeled rate of 1 kcal/min.

Predictions from the Model

The above hypothetical system generates predictions of feeding behavior and body energy increments solely on the basis of interacting physiological components whose functions and values have been specified by experimental data. Earlier feeding models have not achieved this empirical reduction. We believe physiologizing in psychology to be more often pernicious than helpful. Nevertheless, in this case it works.

Intact Freely Fed Rat

The predictions of *ad libitum* feeding from Mark 2D, using the same data as Mark 1, are almost identical to those of the model without distension and the small circadian heat output cycle (21). Using the more recent data on gut clearance and respiration specified above, phasing the slowing of clearance immediately after dawn, and setting chow at 3.2 kcal/g for Le Magnen's laboratory, the model predicts real behavior quite precisely: night intake 13 g and day intake 3.8 g [14 g and 3.5 g observed (23)].

A determinate model with stationary physiological functions naturally predicts unrealistically low variance. Feeding is subject to competition from other activities and motivations. In most laboratory conditions, feeding is also subject to facilitation by random arousing exogenous stimuli. Noise in the feeding onset threshold would roughly model these influences until there are useable theoretical accounts of them. Variation also enters the feeding offset threshold by learning (see below). These additions to the model (creating Mark 3) should produce realistic variability in feeding parameters with little alteration in the already realistic mean values.

Feeding Following Food Deprivation

Unfortunately, there are no respiratory data for rats unexpectedly deprived of food. After 12 hr of daytime deprivation, lipolysis should be substantial, perhaps 10 cal/min. Onset of feeding very rapidly builds up lipogenesis—linearly over 25 min to a value of 35 cal/min—which persists for some time. Mark 2D (Fig. 3) predicts a meal of 4.0 g on refeeding at the start of the dark phase, and an interval of 116 min to the next meal. Values of 4.0 g and 110 min have been reported for real rats (30).

In the model, distension contributes to satiety onset with a meal of that size, although metabolism still has some influence. The size of the first meal on refeeding increases rapidly with recycling through a deprivation schedule (30). Learned desatiation (see below) would explain this, perhaps also with gastric adaptation. When the Mark 2 model allows merely for the metabolic adaptations (23), it does not predict the very large meals observed. Extended prior deprivation eliminates the satiating metabolic effects of recently ingested nutrient (2; see above). It is eccentric (31) to extrapolate to reasonably nourished rats the results of experiments in rats adapted to recovery from starvation.

The model quantitatively substantiates some of Le Magnen's (23) suggestions about the effectiveness of lipolysis at inhibiting hunger. The peak of lipolysis during the day in the freely fed rat is indeed sufficiently high on the earlier data (22) to suppress hunger until the gut is nearly empty and even then to permit only a small meal. An otherwise normal rat chronically force-fed and then left, loses fat at a rate of more than 20 cal/min. Even if metabolic rate remains as high as 40 cal/min, this abnormal lipolysis is sufficient to keep energy flow above the threshold for feeding onset in the model. Thus energy flow explains the anorexia after fattening by insulin, electrical stimulation, or tubing. It could also explain much of cachexic anorexia (32).

VMH Lesions

Mark 1 of the model qualitatively predicted many of the features of feeding behavior in the dynamic and static phases of VMH obesity (18). Mark 2D

predicts similar behavior when recently reported respiratory data (23) are substituted for the assumed lipogenesis values of Booth and Toates (18). The onus of proof is now placed on any claim that ventromedial hyperphagia is entirely a behavioral abnormality. However, we lack sufficient physiological data for the model to determine if the food intake changes can be entirely accounted for by physiological consequences of the autonomic and endocrine effects of the lesions. Circadian metabolic variations can be estimated from Le Magnen's respiratory data (23), but nobody yet has gut clearance functions for VMH preparations. When normal gut functions are assumed (18), neither Mark 1 (18) nor Mark 2D predicts as extreme an increase in food intake and precisely the same distortion in meal pattern as generally seen. According to the model, abnormalities in sensory reactivity (as expressed in changed feeding rate) do not produce sufficiently dramatic differences in intake. Sensory-dependent hormonal effects are already allowed for by the metabolic data. The evidence is against substantial changes in feeding offset thresholds (see above). We predict that one of the next primary effects of VMH lesions to be discovered will be abnormal gastrointestinal control, even when weight and feeding pattern are normalized. Mark 2D with respiratory values from VMH rats (23) and the same clearance rate by day as by night (0.8) predicts a realistic 15 g daytime intake in much more realistic 2.5 g meals (2.7 g with no distension loop) at 122-min intervals.

This discussion illustrates an important merit of quantitative control theory —reciprocal feedback interactions are mechanically calculated. Verbal theorizing about the effects of feeding on lipid metabolism and the effects of lipid metabolism on feeding can sound circular. Intuitions on the net properties of the hypothetical system are easily doubted. Computer models are neither an entertaining luxury nor a fearful bogey in physiology and psychology. They will increasingly become a necessity in theory construction and testing.

Long-Term Regulation of Energy Exchange

The predicted energy increment varies little from day to day in the present model, and the cumulative average daily increment is highly stable. The value of the average increment would be further stabilized if the net energy supply to the receptor system controlling feeding was even weakly coupled to the size of the body energy store or in particular to the amount of triglyceride in adipose tissue. If, for example, large cells leaked glycerol faster or if as triglyceride content rose above a certain level insulin became rapidly less effective at reversing lipolysis, the present model would adjust food intake to limit adiposity. The characteristics of this long-term regulation cannot of course be stated until such a physiological mechanism has been identified in a form that can be modeled and the relevant computations run; yet the qualitative tendency is clear.

Note that such a system does not rely on an accurate signal of fat store size. Neither stability nor precision requires a signal to the nervous system which is independent of the general metabolic signal reflecting net energy flow to receptor-like tissues.

Regulation with No Set-Point Mechanism

The stability of such a system of fat store size could be mathematically equivalent to a set-point function, but there is no set-point mechanism involved, no receptor specific to a signal from the fat store, no system to generate a precise reference value, and no comparator mechanism to compute the error value. If stable or defended value is meant, the term set point should not be substituted because presuppositions from engineering then encourage experimenters to look for unnecessarily complex systems in biology. To regulate body weight, a male rat would need a clock to say what age it was, a map of its proper growth curve (yet to be satisfactorily described mathematically!), a sensor—in the soles of its feet (33)?—of its current body weight, and a reading mechanism to compare them all. There is no evidence for regulation in this sense. Simple physical properties of different parts of the body can readily maintain the powerful observable homeostasis and homeorhesis. For example, if the rate of intestinal absorption of an unmetabolized substance is a decreasing function of its blood concentration and the rate of renal excretion is an increasing function of blood concentration, then blood concentration of that substance will return rapidly and precisely to a preferred value determined by those transport characteristics at widely separated sites, with no receptors and no communication—let alone comparison and error-correcting feedback.

The productive question is likely to be how the metabolite flow into and out of adipose tissue is influenced by the amount of triglyceride in the tissue, not how the brain could build a precise representation of the amount of fat in the body and adjust behavior according to some standard. An energy flow theory can, for example, explain the VMH syndrome without any body-weight set point, let alone two set points and postulated splits of a unitary system into drive and incentive components (34, 35). Energy flow into fat because of taste-triggered endocrine reactions would explain short latencies and large meals on palatable food *ad libitum*. Energy flow from fat during acute deprivation would explain poor motivation (see deprived rat, above) and its normalcy in slimmed VMH rats.

INDIRECT METABOLIC CONTROL

Functional analysis of the asymptotic performance of a fully adapted system tells us little of the processing or structure which directly controls behavior. The relative success of the feeding model for rats adapted to a single familiar

diet is not evidence that hunger is under direct instantaneous control by variations in current energy supply to tissues. Such close adaptation to current supply could be achieved by behavior that depends on interpretation of present events according to past experience of their consequences for energy flows.

Acquired Sensory Control of Energy Intake Rate

Long-established conditioned or learned reactions to orosensory cues in anticipation of energy yield could be a major determinant of chow-eating rate. Ingestion of solids in the infant (14), adult taste preferences (12) and aversions (13, 36, 37), and the operant or adjunctive lever-press to feed intravenously (38) all appear to be acquired largely by energy yields conditioning the reactions of the rat to sensory or internal sensations. There is some relation between the two-stimulus preference for a diet and the rate of ingestion of that diet alone (39, 40). This effect may not greatly influence single-diet intake rate, except at extremes of palatability. When a choice of foodstuffs is provided, however, energy-conditioned preferences would strongly influence the average rate of energy intake during the meal. In the model, a change in energy input rate has definite although small effects on meal size and other variables.

Acquired Sensory Control of Satiety Threshold

One of the most remarkable statements in the model is that the major contribution to the inhibition of feeding that ends a meal *ad libitum* comes from the energy flow of absorption. It has often been assumed that gastric clearance and intestinal digestion are too slow for absorbed nutrients to make any contribution to the onset of satiety. This alternative extreme is certainly false. Relevant findings in man have already been mentioned. Radioactivity from starch taken on an empty stomach has begun to be digested, absorbed, and transported into the rat brain in much less than 5 min from the start of ingestion (41). With some food from the previous meal still in the stomach, at least the initial parts of the new meal mostly pass immediately into the intestine, which contains abundant enzymes under those conditions.

Thus absorption starts very early and can gather pace extremely rapidly. Nevertheless, the physics of transporting energy from the mouth to a receptor tissue would impose a delay of many seconds between final ingestion and peak absorption, even if the biochemistry and physiology did not expand it to 2 to 10 minutes. Introducing such a lag into the absorption loop of the model would produce much larger meals.

If the success of the model truly reflects the ultimate controlling factor in feeding, real rats must be anticipating peak energy absorption. Engineers use acceleration rather than rate, a principle that has been suggested for satiety

(15, 42). The initial pulse of insulin secretion could amplify the submaximal flow of glucose at an insulin-sensitive receptor. What certainly does occur in the rat is the acquisition and maintenance of oral sensory control of the end of a meal, reinforced or conditioned by the eventual rate of carbohydrate absorption (13, 37). The effect may be purely central or it could be mediated by conditioned oral control of insulin secretion (43).

Addition to Feeding Model

The phenomenon could be represented in the model as a sensory driving of a reduction in the off-threshold by the amount that peak absorption exceeded 20 cal/min on previous occasions following ingestion of food having that sensory quality. Meal size would then approach that producing a peak absorption of 20 cal/min after some delay (Mark 3).

Acquired Sensory Satiety in Man

People also rapidly acquire feeding offset differentiation according to previous experience of the after effects of ingesting food of a particular flavor (44). Differential aftereffects were generated by disguised starch loads immediately before the otherwise normal sandwich lunches. Most of the acquired sensory control of meal size was vested in the unfamiliar flavor possessed by a slightly modified yogurt dessert (Fig. 4). The response was not deliberate, even if it was instrumental: conditioned subjects did not seem to be aware of their differentiation of behavior, nor did they consistently report any perception of the dessert or the starch load which could account for the anticipatory use of the flavor cue. Nevertheless, such differentiation is likely to enter awareness in some cases or in due course, and we would not doubt that an element of thought and calculation can and often does enter the control of human feeding.

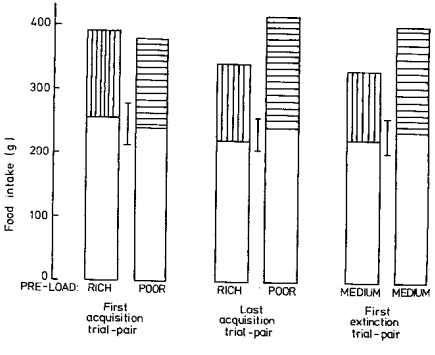

FIG. 4. Acquired oral control of satiation in man (44). Each column is mean lunch size under one condition ($n = 8$). A load which was rich, poor, or medium in starch content was given immediately before lunch. Vertical hatching, intake of dessert of a flavor following the rich load during acquisition; horizontal hatching, flavor paired with poor load; vertical line, SD of difference in amounts of dessert taken (this difference and total meal size difference at last acquisition lunches and first extinction lunches, $p < 0.01$).

The sensitivity of these people's feeding behavior to postprandial consequences was sufficient to establish an anticipatory response difference almost equal in energy to the energy difference imposed in the starch loads. Clearly, this behavior cannot coherently be described as a straight summation of internal (or drive) influences and external (or incentive) influences. The two are in continuous cognitive interaction, in or out of awareness. Systematic training according to this acquired sensory satiation paradigm could be at least as helpful in weight control as the use of direct subjective effects of starch loads suggested earlier. Anticipatory control of feeding offset may be particularly important for man in societies like ours, because other behavioral mechanisms for regulating energy balance have little chance to operate—social factors largely determine feeding onset and the size of a meal is often fixed at its beginning when the plate or tray is filled.

EXTENSIONS OF THE PHYSIOLOGICAL CONTROL THEORY

This simplified quantitative theory, particularly when elaborated to include learning and other refinements of the sensory control of feeding, may be applicable to economically or clinically important problems.

Ruminant Model

Physiological data on gut contents and the energy flow from absorption of short-chain fatty acids are available for sheep and other economically important ruminants. The thus far successful inclusion of a distension loop in Mark 2 for the rat encourages the hope that these theoretical principles will prove to be applicable with the diets of low-energy density common in animal production (45–47).

Human Model

It is ethically and technically feasible to obtain estimates of energy flows in lean or obese subjects that would provide a data base homologous to that used in the rat model. The physiological reduction of human hunger could then be attempted. Given the data and arguments on human feeding presented in this chapter, it is quite conceivable that some realistic predictions will be possible, at least in lean subjects, from a model that allows for indirect as well as direct metabolic control, and specifies many social factors as limits on the availability of food. The model could well give the most illuminating account yet of the unfortunate and complex interactions between behavior and physiology in the obese subject. In principle, it might provide an individually tailored specification for an optimum and stable feeding schedule at which behavior modification could be aimed.

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HUNGER

Basic Mechanisms and Clinical Implications

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Conclusion