fully has been solved. When the development is completed, the Faraday cage will be used as the basis for calibration of all the current-measuring devices sent to NBS for calibration at high levels of current, energy, and power.

Two specific recent discussions with groups of users have been initiated to develop electron-beam techniques and measurement recommendations. A committee of the American Society for Testing Materials, chaired by D. Trageser (*28*), has formulated a list of electron-beam parameters (current, energy, beam profile and size, and scan width and speed) that must be defined and measured for accurate application of electron beams in industry. A committee of the American Association for Physicists in Medicine, chaired by J. S. Laughlin (*29*), has developed a protocol for measurements of absorbed dose and electron output that are required in medical therapy. The Bureau is actively participating with these two groups and with others in developing a sound philosophy and procedure for measurement of electron beams.

References and Notes

1. A standard for radiation measurements may be a physical representation of a unit of a fundamental radiation quantity, or a device or a procedure that provides a measure of a unit of the quantity. Standards for measurement of radiation are usually standards defined by agreement; they are also usually derived standards that can be expressed in terms of the six base standards for the quantities of length, mass, time, current, temperature, and luminous intensity. Examples of radiation standards are total-energy ionization chambers for measuring energies of x-ray beams in joules, and radioactive sources of neutrons for defining a neutron-emission rate. The category of radiation standards includes nuclear standards.
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Regulation of Food Intake and Obesity

The regulation of food intake is complex; a number of abnormalities may cause obesity.

Jean Mayer and Donald W. Thomas

Understanding of the physiological determinants of feeding behavior and their phenomenal correlates—hunger, appetite, and satiety—has for centuries challenged students of varied disciplines seeking to solve practical problems and resolve theoretical issues. Philosophical speculation and limited physiological evidence at first suggested that food intake is controlled by specific peripheral sensations which reflect the state of the stomach and gut and determine the subjective level of hunger. In recent years more sophisticated research techniques have revealed a powerful and complex central regulatory system, one capable of closely matching energy intake to energy expenditure in the face of marked variations in the energy requirements of the organism and the nutritional value of the diet. Although transient factors may momentarily override its control, this central system normally prevails, maintaining the energy balance of the organism with remarkable accuracy.

When for some reason this balance is upset in such a way that energy intake consistently exceeds energy expenditure, the inevitable result is obesity—the accumulation of excess body fat, once prized in certain societies but now recognized as a major public health problem. Although some cases of obesity are attributable directly to failure of the central regulatory mechanism, others may be the single end result of neurological, endocrine, enzymatic, and psychological conditions which have very little in common. Thus, the regulation of food intake and obesity, the topics of this review, represent problem areas which are in a sense relatively independent and, therefore, can most conveniently be discussed separately, but which overlap and interact in a complex manner.

Hunger and Regulation

Ancient philosophical speculation suggested that the feelings of hunger assumed to control food intake originated in the abdominal cavity when-

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ever the alimentary canal became empty. A more specific hypothesis was offered by the great physician Galen (A.D. 138–201), who identified the stomach as the primary seat of hunger and attributed the pangs and gnawing sensations which accompany prolonged lack of food to contractions of that organ. This view survived into the 18th century, when Haller, the first physiologist to write at length on hunger and thirst, ascribed the desire to eat to (i) "intolerable pain" due to the rubbing against one another of the folds of the empty stomach and (ii) recollection of the pleasure associated with eating. Although similar "peripheral" or "local" theories (that is, theories which attribute hunger to the stimulation of peripheral nerves, mainly in the stomach) were proposed in the 19th century by such prominent scientists as Erasmus Darwin, Johannes Müller, and Weber, two newer types of theory began to compete for acceptance. In the "central origin" theory, Magendie, Tidewald, and Milne-Edwards postulated that a "hunger center" located in the brain is directly sensitive to the depletion of nutrients in the blood. In the "general sensation" theory, Roux and Michael-Foster suggested that a lack of nutritive material in the blood stimulates a central hunger center indirectly through afferent impulses arising from all organs of the body.

By the turn of the century, important conceptual and methodological advances provided new evidence concerning the physiological mechanisms which control food intake. In 1901 André Mayer (*1*) published a study on thirst which represented the first application to the study of feeding and drinking of Claude Bernard's concept of physiological regulation. Although recognizing the great importance of sensory phenomena in thirst, André Mayer demonstrated that the regulation of water intake could be conveniently studied in animals by circumventing these sensations. Water intake and water losses could be measured, and drinking behavior could be related to overall water balance and to such measurable physiological indices as the osmolarity of blood solutes. Similarly, while André Mayer was aware that complex psychological factors were involved in the urge to eat and recognized the probable complexity of the psychological factors involved in the process of feeding, he later showed that, by determining the food intake, the energy expenditure, and the variations of the body reserves, it was possible to demonstrate that the food intake was regulated so as to maintain the homeostasis of the body (*2*). Further, this regulation could be shown to operate through two mechanisms: (i) a short-term regulation which, on a daily basis, roughly balances caloric intake with energy expenditure as the amount of food required varies due to changes in activity, in the temperature of the environment, and in composition of the diet, and (ii) long-term regulation which, over a much longer period, corrects the errors of the short-term mechanism. Both regulations, he found, could be described in mathematical terms by measuring such characteristics as precision, consistency, sensitivity, and rapidity. [This approach has been used recently by Rozin and J. Mayer (*3*) to demonstrate the existence of a food-intake regulation in the goldfish and to characterize its mode of action.] Thus, the problem was no longer simply that of identifying the physiological origins of the sensations of hunger but, rather, was that of discovering a physiological mechanism capable of precisely regulating food intake so as to maintain the energy balance of the organism.

Search for a Mechanism

During the first quarter of this century, the well-entrenched "peripheral" theories continued to influence the search for a regulatory mechanism. In 1912 Cannon and Washburn (*4*) demonstrated conclusively that, in man, hunger "pangs" coincide with trains of gastric "hunger" contractions. Carlson (*5*) soon confirmed and extended these observations in experiments described in his well-known book *The Control of Hunger in Health and Disease*, and further suggested that the level of blood glucose controls gastric motility and hunger. Although during several decades the writings of Cannon and Carlson were widely accepted as an experimental basis for local regulation of food intake, enough contrary evidence has been accumulated to render any theory of regulation primarily based upon gastric motility untenable today.

Adolph (*6*), for example, showed that increasing the bulk of an animal's ration through the addition of nonnutritive material, a procedure which has considerable effect on gastric motility, has only a very transient influence on food intake. Grossman and Stein (*7*) demonstrated that neither vagotomy nor splanchnectomy—procedures which drastically alter the occurrence and phenomenal experience of gastric contractions—had an appreciable effect on intake. Perhaps the most striking evidence against the "local" theory is provided by reports of individuals who continue to experience the sensations of hunger and to maintain their normal intake of food after their stomachs have been surgically removed (*8*). It is now evident that stomach contractions may at times contribute to the sensation of hunger but do not play a major role in the normal regulation of food intake.

Methodological difficulties associated with investigation of the central nervous system delayed development of central theories of regulation. Preliminary observations by Camus and Roussy in 1913 and by Bailey and Bremer in 1921 suggested that the extreme obesity observed in patients with the so-called Fröhlich syndrome was due to hypothalamic lesions. However, it was not until the 1940's that improved surgical techniques enabled Hetherington and Ranson to demonstrate that, in the rat, obesity regularly follows bilateral electrolytic destruction of the ventromedial nuclei of the hypothalamus. Brobeck and his colleagues soon replicated these observations and, finding that the obesity could be attributed almost entirely to increased food intake, termed the syndrome "hypothalamic hyperphagia" (*9*). J. Mayer and his coworkers subsequently showed that similar electrolytic lesions produce obesity in the mouse, while other investigators confirmed the phenomenon in a variety of species, including cats, dogs, and monkeys (*10*). Epstein has demonstrated that bilateral anesthetization of the ventromedial area is sufficient to elicit normal feeding behavior in satiated rats (*11*). Baile and J. Mayer have recently shown (*12*) that anesthetization (or bilateral destruction) of this area causes hyperphagia in ruminants as well.

In his early work, Hetherington noted that lesions in the area immediately lateral to the ventromedial nucleus were also sufficient to produce hypothalamic obesity. In 1951 Anand and Brobeck confirmed this observation and discovered that bilateral destruction of a more lateral hypothalamic area caused animals to become aphagic (*13*). Moreover, they demonstrated that even animals made hyperphagic by ventromedial lesions become aphagic follow-

ing destruction of these lateral areas. Discovering that these findings observed in rats hold true for cats and monkeys as well, Anand and his colleagues postulated a hypothalamic feeding system involving the ventromedial nucleus, the ventrolateral area, and the nerve fibers connecting these two neural centers (*14*). In this system the ventrolateral area would be a "feeding center" responsible for the urge to eat or the initiation of feeding, while the ventromedial nucleus would be a "satiety center" capable of exerting inhibitory control over the lateral feeding center. A variety of behavioral and physiological evidence has since confirmed the existence of such a system and elucidated the functions of its components.

Behavioral Evidence

In an early application of operant techniques to the study of feeding, Anliker and J. Mayer trained both normal mice and mice that were hyperphagic as a result of lesions of the ventromedial area of the hypothalamus to obtain food pellets by pressing a lever. They found that bilateral destruction of the ventromedial nuclei did not result in an increase in the rate of lever pressing, a generally reliable correlate of hunger, but that hyperphagic animals spent too much time eating at a more-or-less normal rate (*15*). Using a liquid diet of greater caloric density, Teitelbaum and Campbell (*16*) soon demonstrated that the excessive food intake of the hyperphagic rat could be attributed to an increase in the size of the meal rather than to an increase in the frequency of feeding. We have recently completed a series of experiments which confirm these findings and, further, demonstrate that, for both normal and hyperphagic rats, the duration of a period of satiety is highly correlated with the size of the preceding meal but apparently does not affect the size of the meal which follows. In addition, we found that equal increments in the size of the meal resulted in comparable increases in the duration of postprandial satiety in normal rats and in rats with ventromedial lesions; thus the excessive intake of the hyperphagic animals appeared to be attributable to a relatively constant delay in the termination of feeding (*17*). We also examined rates of bar pressing for food over the course of individual meals eaten by normal and hyperphagic rats. Preliminary analysis suggests that normal rats press the bar at a relatively constant rate throughout the meal, then abruptly terminate feeding, while animals with lesions of the ventromedial hypothalamus begin pressing in a similar manner but end their very large meals through a gradual reduction in the rate of bar pressing. These observations may be interpreted as evidence that damage to the ventromedial hypothalamic nuclei results in impairment of the mechanism of satiety—evidence which is in accord with the postulated role of these areas in the hypothalamic regulation of food intake.

Other behavioral evidence has long suggested such an interpretation. While food intake remains excessive throughout the development of obesity, the strength of motivation underlying the feeding response of the hyperphagic animal soon wanes to a level below that of a comparable normal animal. Working with moderately obese animals, Miller, Bailey, and Stevenson (*18*) found that a decreased motivation for food in the hyperphagic animal is evident not only from a relatively low rate of bar pressing for food but also from inferior performance on other behavioral tests, including measurement of the animal's speed of running down a short alley to secure food; of the pull the animal exerts during temporary restraint as it approaches food; of the amount of electric shock required to prevent it from approaching food; and of the amount it eats when it must lift a weighted lid to gain access to food. Teitelbaum (*19*) demonstrated that although the experimental animals in the initial phase of hyperphagia, like normal animals, maintain appreciable food intakes despite adulteration of their diet with cellulose or quinine, which make it less palatable, obese animals show almost complete rejection of diets adulterated with such substances. Moreover, even the change in texture resulting when powdered food was substituted for the pellets usually offered an obese hyperphagic animal caused a marked decrease in food intake. It thus appears that, in the late phases of hypothalamic obesity, animals become finicky eaters and hypersensitive to the negative-stimulus aspects of the diet. Kennedy (*20*) has observed similar finickiness in old, relatively fat, normal rats and suggests that such behavior signals the approach of satiety mediated by a lipostatic regulatory system.

The fact that hyperphagics, unlike normals, respond to greater palatability of the diet with marked increases in food intake further supports the hypothesis that hyperphagia represents a failure of satiety (*19*). Since hyperphagic animals tend to be very responsive to the positive-stimulus aspects of their diet, it is reasonable to ask whether this sensitization is the basic motivational factor underlying the excessive food intake which follows surgical destruction of the ventromedial area. Preliminary experimental evidence obtained by McGinty, Epstein, and Teitelbaum (*21*) indicates that this is not the case. When required to feed themselves by bar pressing for food injected through permanently implanted gastric tubes, animals with ventromedial lesions eventually overeat and become obese in the absence of any oropharyngeal sensations, although, under these conditions, the rate of weight gain is low and high levels of obesity are not attained. Moreover, once these intragastrically fed animals have reached their plateau weight, addition to the diet of a small amount of saccharin which they can ingest orally results in new bouts of feeding and a rapid increase in body weight. Thus it appears that excessive responsiveness to highly palatable food is not the cause of hyperphagia associated with hypothalamic lesions, but oropharyngeal sensations acting in the absence of the normal satiety mechanism apparently do determine the rate and duration of overeating and are essential for development of maximum levels of obesity.

The application of behavioral techniques in conjunction with the methods of physiology has also contributed to our present understanding of the way in which the lateral feeding center functions. Although lesions of the lateral hypothalamus cause both aphagia and adipsia, Morrison and J. Mayer (*22*) were able to show, through careful plotting of "aphagic" and "adipsic" lesions and comparisons of the behavior of animals having true lesions with that of animals which had undergone sham operations, when all the animals were deprived of food or water, that feeding and drinking are controlled by different neural centers. Teitelbaum and his associates have demonstrated that animals recover from lateral hypothalamic lesions if they are maintained by tube feeding during the initial period of fasting, and that this recovery takes place in a regular and orderly manner. These ani-

mals at first accept only wet and highly palatable foods, then, if hydrated by gastric tube, eat dry food, and finally drink water and eat their usual dry ration (*23*). This evidence, in conjunction with the observation that aphagic animals do not take advantage of the opportunity to feed themselves through an implanted gastric tube, suggests that damage to the lateral hypothalamus produces a motivational deficit rather than a motor failure (*24*). This motivational function is further evidenced by the fact that stimulation of the lateral hypothalamus not only causes satiated animals to eat and to become obese but can motivate animals to perform a previously learned response, or to learn a new behavioral act, in order to obtain food (*25*). Thus, the lateral hypothalamic area appears to be an integrative center which links the neural correlates of hunger and appetite with the feeding response system.

The Glucostatic Component in Regulation of Food Intake

It is important to know how this hypothalamic regulatory system monitors the nutritional state of the organism. In the early 1950's, one of us (J.M.) postulated the presence of chemoreceptors located in the ventromedial hypothalamic nuclei, and perhaps in other central and peripheral areas as well, which have a special affinity for glucose and are activated by this metabolite in the measure that they utilize it. Obviously the *level* of glucose alone is not the activator, as indicated by the ravenous appetite of diabetics. A corollary to this hypothesis was the postulate that the pattern of glucose utilization of ventromedial glucoreceptors would be found to be more similar to that of extrahepatic tissue than to that of other areas of the brain, and that these glucoreceptors would, in particular, show some sensitivity to insulin. The "glucostatic" hypothesis was based in part on the observation that carbohydrate reserves are proportionately much more depleted between meals than are reserves of protein or fat. Further, since glucose metabolism, which is regulated by a complex endocrine machinery, is itself a regulator of fat and protein utilization and synthesis, a mechanism of regulation of food intake based on the monitoring of glucose utilization could be readily integrated with energy metabolism and its components.

In an early effort to test this theory, J. Mayer and Van Itallie established an excellent correlation between overall glucose utilization, measured through arteriovenous differences in glucose concentration (Δ-glucose), and the presence or absence of gastric contractions and sensations of hunger (*26*). A large Δ-glucose value was observed to be coincident with satiety, while evidence of hunger feelings and gastric contractions were seen only in states of low glucose utilization (a small Δ-glucose value). Apparent exceptions could be satisfactorily interpreted on the basis of changes in circulation dynamics, rapid rises in blood glucose, certain effects of insulin, and the presence of overriding, dominant conditioning. Similarly, Stunkard, Van Itallie, and Reiss demonstrated in human subjects that small doses of glucagon, a pancreatic hormone which raises both blood glucose level and Δ-glucose, consistently eliminate gastric contractions and feelings of hunger (*27*). This effect was confirmed in the rat by J. Mayer and Sudsaneh (*28*), who further noted that inhibition of gastric contractions occurred only after blood glucose had risen substantially. This comparative study also showed that doses of glucagon uniformly effective in inhibiting gastric hunger contractions in normal rats no longer inhibit such contractions if the ventromedial area has been destroyed, even though the pattern of fasting contractions of such animals is normal, as is the inhibitory gastric response to such locally active agents as epinephrine and norepinephrine. It thus appears that the ventromedial area exercises a measure of control over gastric hunger contractions (probably through Schutz's bundles and the vagi) and does so in response to an increase in glucose utilization. Recent work by Ridley and Brooks (*29*) suggests that a similar hypothalamic control mechanism may be operating in the control of gastric secretion.

A more direct demonstration of the special affinity of the ventromedial nuclei for glucose was provided when J. Mayer and his co-workers (*30*) showed that injections of gold thioglucose sufficient to produce obesity selectively destroy cells in the region of the satiety center. These investigators further demonstrated that injection of compounds in which the gold thiomoiety is linked to metabolites other than glucose (gold thiomalate, gold thiogalactose, gold thiosorbitol, gold thioglycerol, and so on) produce neither ventromedial hypothalamic damage nor obesity (Figs. 1 and 2). It appeared

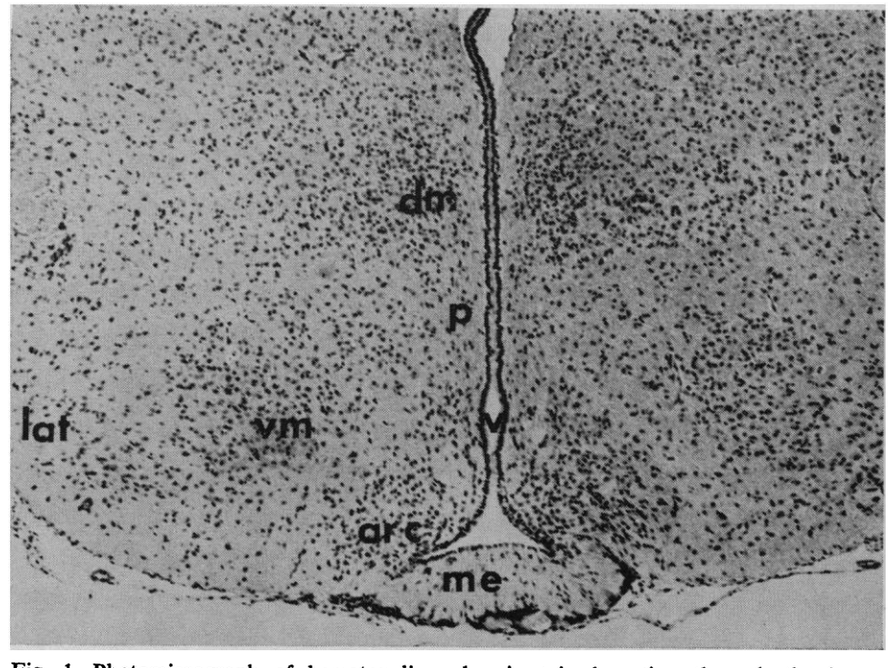

Fig. 1. Photomicrograph of hematoxylin-and-eosin-stained section through the hypothalamus of a mouse that had been treated with gold thiomalate. The photomicrograph indicates a normal hypothalamic nuclear configuration and a normal number of neurons. The labels indicate normal landmarks and nuclei seen in this region of the hypothalamus: *dm*, dorsomedial nucleus; *p*, periventricular region; *v*, third ventricle; *vm*, ventromedial nucleus; *lat*, lateral hypothalamic area; *arc*, arcuate nucleus; *me*, median eminence.

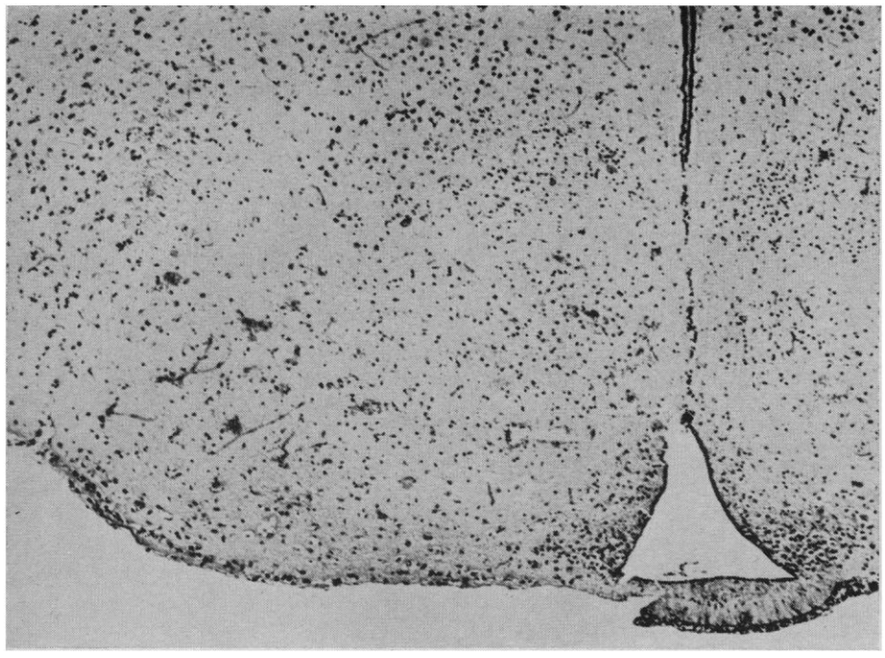

Fig. 2. Photomicrograph of a section of the same hypothalamic area as that of Fig. 1, from a different mouse, after administration of gold thioglucose. Note the marked loss of neurons and the presence of pyknotic cells in the ventral part of the hypothalamus. The normal hypothalamic nuclear pattern has been lost. Punctate hemorrhages can be seen in the left lower quadrant. The upper left corner and upper segment of the photomicrograph show areas of normal tissue. The rest is visibly edematous.

that accumulations of gold reached toxic levels in the ventromedial area only if that moiety were drawn in by glucose, a hypothesis since confirmed through the use of radioautographic and neutron-activating analytical techniques by Debons and his associates (*31*). Injecting gold thioglucose in combination with glucose appears to increase uptake of the toxic substance by glucoreceptive cells (*32*). Thus glucose itself may have an enhancing effect, due perhaps to its role in dilating capillaries or increasing their permeability. Edelman has offered an interesting theory of satiety according to which inhibition of the lateral feeding center increases as greater numbers of glucoreceptors of decreasing sensitivity are brought into action. He further suggests (*32*) that generation of an action potential in a particular ventromedial neuron depends upon the metabolism of a specific quantity of glucose in a glial cell, and that there are different rates of glucose supply to, or different intrinsic rates of glucose metabolism in, the various neuron-glial complexes of the satiety area.

A number of recent experiments have confirmed the postulated metabolic heterogeneity of the hypothalamus and the special metabolic characteristics of the ventromedial area. Forssberg and Larsson had shown (*33*) that the uptake of P^{32}- and C^{14}-labeled glucose by this area was much more dependent upon the state of nutrition of the animal than uptake by other hypothalamic areas was. Subsequent studies by Chain, Larsson, and others (*34*) have extended these findings by showing that C^{14}-labeled glucose is incorporated into a variety of compounds in this area. Anand has found (*35*) that in fed animals the glucose and oxygen uptake per unit of nucleic acid is greater in the ventromedial area than in the lateral area, and that the situation is reversed in the starved animal.

Recordings of the electrical activity of cells within the hypothalamus have provided additional support for the concept of glucostatic regulation. Anand and his colleagues found that the induction of hyperglycemia resulted in a general increase in the activity of the ventromedial area with some concomitant drop in the activity of the lateral area. Conversely, hypoglycemia decreased the activity of the ventromedial area and occasionally increased the activity of the lateral hypothalamus. No change in the activity of other hypothalamic or cortical areas was noted. Moreover, intravenous infusion of fat or protein did not alter the activities of the ventromedial, lateral, or other regions of the hypothalamus. Recent studies of single unit activity in the satiety and feeding centers have shown a striking positive correlation between glucose utilization and activity of individual ventromedial neurons and a reciprocal response pattern among cells of the lateral hypothalamic area (*36*).

Long-Term Regulation of Food Intake

While the glucostatic mechanism appears to provide a coherent account of the day-to-day regulation of food intake, it may be that long-term regulation is dependent upon a lipostatic mechanism which acts to inhibit food intake whenever sufficient energy is derived from the mobilization of surplus body fat. Because of the relationship between glucose utilization and the release of free fatty acid, long-term regulation may well act through modifications of the glucostatic system. Such a mechanism would, in effect, regulate body weight by correcting errors in short-term intake through successive recompensations. It would also account for the voluntary fasting of normal animals made obese through force-feeding or insulin-induced hyperphagia (*37*) and for the eventual limitation of weight gains following surgical production of ventromedial hypothalamic lesions.

Limiting Mechanisms

Under exceptional circumstances other hypothalamic "safety valves" may defend the organism by temporarily limiting food intake. For example, Krauss and J. Mayer have shown (*38*) that such factors as high protein levels or amino acid imbalance activate a mechanism which shuts off food intake but does not act through the ventromedial area and is not instrumental in adjusting energy intake to energy output. Similar mechanisms respond to conditions such as pyrexia, dehydration, and gastric distention. Although these protective devices occasionally inhibit feeding, the fact that animals usually maintain constant caloric intake despite wide variations in the composition of their diet and in the oropharyngeal sensations which accompany feeding indicates that other, regulatory mechanisms ordinarily control food intake.

Peripheral Determinants of Meal Size

Although it is well established that central rather than local mechanisms bear primary responsibility for regulating daily food intake so as to maintain the energy balance of the organism, peripheral chemoreceptors may play an important role in determining the size of individual meals. A principal criticism of theories emphasizing central regulation of food intake has been that they do not provide an adequate explanation of the speed with which phenomenal and physiological indicators of satiety respond to the ingestion of food. Meals are always ended long before all of the ingested nutrients are absorbed. Moreover, the experience of satiety which commonly follows the ingestion of food is often so immediate that no significant absorption of nutrients can have occurred. At the physiological level, rises in blood glucose following ingestion of food appear to be too rapid to be accounted for by absorption from the digestive tract (*39*). Through labeling with radioisotopes, J. Mayer and Rupe (*40*) have demonstrated that this initial rise in blood glucose is attributable not to the absorption of glucose from the ingested food but to release of endogenous glucose from hepatic stores.

While it is possible that oropharyngeal sensations may have some effect upon humoral responses, sham-feeding experiments, in which swallowed food leaves the body through a fistula before reaching the stomach, indicate that the mere consumption of food is not effective in producing satiety (*41*). Increasing evidence points to the operation of gastric receptors, perhaps peripheral glucoreceptors, sensitive to the nutritive value of ingested foods. Gastric loads of glucose delivered by stomach tube produce almost immediate satiety in the rat (*42*). Moreoever, there is a higher plasma insulin response to glucose given jejunally than to glucose given intravenously (*43*). Such preabsorptive responses could be mediated by glucagon, a pancreatic hormone which increases both the level and the utilization of blood glucose.

We have recently completed experiments which may be interpreted as further evidence of peripheral energy sensing. Records of meal size under free-feeding conditions were obtained for rats trained to secure their daily ration of liquid food by pressing a bar. The delivery system was then modified in such a way that each bar press provided the usual amount of liquid food for oral consumption plus an equal quantity, of twice the normal caloric density, delivered directly to the stomach by means of a permanently implanted gastric tube (Fig. 3). The animals adjusted to this condition immediately, taking meals which were equivalent in caloric value to those eaten during the preceding control period but were smaller in volume (and were ingested in only 2 to 4 minutes). Although the short latency of this response suggested the operation of peripheral chemoreceptors, the possibility that the observed decrease in meal size represented an aversive response to the infusion process itself was tested by infusing water rather than concentrated liquid food. Under this condition, animals maintained their normal oral intake at each meal even though twice the usual volume of liquid reached the stomach.

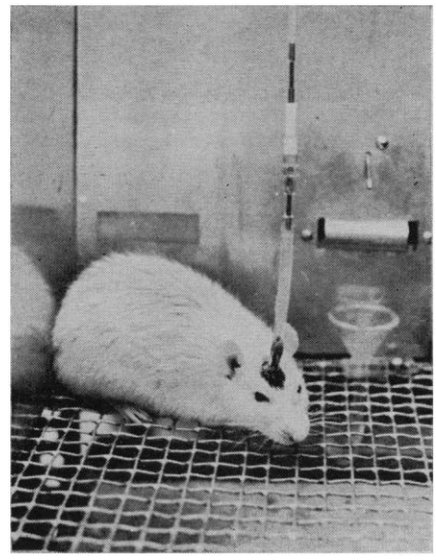

Fig. 3. A rat fitted with a nasopharyngeal gastric tube, shown in a cage used in the study of feeding behavior. When the rat presses the bar at the rear of the cage, liquid food for oral consumption is delivered from a drinking spout, while water or additional food is injected directly into the animal's stomach.

Thus it appears that short-term feedback concerning the nutritive value of ingested foods may be relayed from gastric sensors to the hypothalamic regulatory system by way of neural or humoral paths, or both. This information, added to information concerning levels of available glucose and integrated with the myriad other exteroceptive and interoceptive inputs to the organism at a particular moment, would determine the balance of appetite and satiety and the continuance or termination of the feeding response. Variations in meal size which were attributable to changes in the external situation could be compensated for by appropriate adjustment of the intermeal interval, mediated by the postabsorptive factors sensed by the hypothalamic regulatory system. Cumulative errors in this system could, in turn, be corrected through the long-term, lipostatic regulation. Thus, regulation of food intake may take place in three stages which differ temporally but are integrated in a complementary manner through a single mechanism.

Classification of Obesity

Our concern with obesity thus far has been confined to obesity resulting from trauma to the neural system responsible for the regulation of food intake. However, this is but one of many known obesities, which can be classified from the point of view of etiology (initial causes) or classified upon the basis of pathogenesis (mechanisms of development). The first approach was developed at length in an earlier review (*44*), which distinguished between "genetic," "traumatic," and "environmental" factors in the etiology of obesity. While this distinction was useful, it did necessitate a certain degree of oversimplification. For obesity to develop there has to be a favorable interaction of genotypic factors with a permissive environment, or an interaction of certain traumatic factors with a favorable genetic background, again in a permissive environment.

An alternative classification, based upon mechanisms of development, has also been used by J. Mayer and his associates (*45*). A general distinction can be made between "regulatory" obesities, in which the primary disorder is impairment of the central mechanisms regulating food intake, and "metabolic" obesities, in which the primary lesion is an inborn or acquired error in the metabolism of tissues. It is often difficult to identify the primary abnormality because the persistent hyperphagia and consequent adiposity resulting from regulatory failure may lead to secondary metabolic abnormalities, and, conversely, peripheral metabolic dysfunction may eventually interfere with proper func-

tioning of the central nervous system. However, comparisons between different types of obesity in mice in studies conducted in this laboratory over the past 15 years demonstrate both the validity and the necessity of such a distinction.

Regulatory obesities are exemplified by those, described above, which result from bilateral destruction of the ventromedial nuclei of the hypothalamus, whether produced electrolytically or through administration of gold thioglucose. Mice with these syndromes consume exceptionally large amounts of food and may attain four times their normal weight. Their rates of lipogenesis and cholesterogenesis (as measured by incorporation of labeled acetate, pyruvate, or glucose into hepatic and extrahepatic fatty acids and cholesterol in vivo and in vitro) increase in proportion to the extent to which they are allowed to overeat (*45*). The rate of absorption of glucose by the intestine is increased, but this appears to be secondary to the habitual overconsumption of high carbohydrate diet and does not occur when food intake is restricted or the diet is low in carbohydrate. When the weight of these animals is reduced through underfeeding, lipogenesis decreases and body composition returns to normal as the weight approaches normal values.

The picture is strikingly different in metabolic obesities such as the hereditary obese-hyperglycemic syndrome (*46*), obesity due to the grafting of ACTH-secreting pituitary tumors (*47*), yellow obesity (*48*), and New Zealand obesity (*49*). For example, mice with the hereditary obese-hyperglycemic syndrome (*50*), extensively studied in this laboratory (*45, 46*), are usually extremely hyperglycemic, or the hyperglycemia can readily be elicited by the administration of growth hormone, which has little or no effect on the blood glucose levels of normal mice or of mice obese as a result of hypothalamic lesions. In addition, the obese hyperglycemic mice are hypercholesterolemic and evince a variety of atypical responses to the administration of various hormones. While such "physical" defenses against cold as piloerection and vasoconstriction are made normally, obese hyperglycemic mice are incapable of raising their metabolism when exposed to low temperatures and, therefore, die rapidly in the cold. When their weight is reduced through dietary restriction, obese hyperglycemic mice do not oxidize their fat to the normal extent, burn considerable protein instead, and are thus still very obese even when no longer overweight. Even when they weigh one-third less than their non-obese litter mates, their bodies may still contain twice as much fat. Characteristic behavioral abnormalities are also apparent. Obese hyperglycemic mice will not mate, and they show food choices different from those of non-obese animals or animals obese as a result of hypothalamic lesions. Although their obesity is as extreme as that observed following ventromedial lesions, their hyperphagia is usually less pronounced because the caloric surplus is in part caused by their relative inactivity (*45, 46*).

The obese hyperglycemic animals are characterized also by a hypertrophic pancreas with unusually numerous and large islets of Langerhans, which show mitotic figures and degranulation. In spite of the hyperglycemia, both the pancreatic levels of insulin and the levels of circulating insulin are elevated. When alloxan is administered, the islets become massively regranulated, while blood glucose level decreases to nearly normal values. Caffeine, by contrast, increases blood glucose level for long periods (*45, 46, 51*). None of these phenomena are seen in normal animals or in animals displaying regulatory obesities. Nor are other metabolic and enzymatic abnormalities which are characteristic of the obese hyperglycemic syndrome: increased synthesis of glycogen and fat in the liver and an increase in liver phosphorylase; an increase of coenzyme A in adipose tissue; a tremendous increase, in adipose tissue, of lipogenesis from acetate, even under fasting conditions, together with a decrease in glucose uptake (per milligram of nitrogen) (*46*). In obese hyperglycemic animals, release of free fatty acids by adipose tissue, unlike such release in normal animals or in regulatory obesities, is independent of the nature of dietary fats and insensitive to the effect of epinephrine or of the fat-mobilizing substance (FMS) isolated from human urine (*45, 46*).

It may well be that the basic disorder in these animals is the presence of glycerokinase activity in the adipose tissue, a possibility suggesting that the absence of the repressor to the enzyme, normally present in this tissue, is the genetic abnormality primary to all others (glycerokinase activity is found in other tissues and, hence, is coded in the nucleic acid, but is normally repressed in adipose tissue) (*52*). Normally, in the absence of glycerokinase activity, adipose tissue cannot reutilize glycerol released by lipolysis and must depend upon glycerophosphate provided by glucose catabolism to resynthesize fat. Consequently, lipogenesis in adipose tissue is normally controlled by the availability of glycerophosphate and, indirectly, of glucose. The abnormal presence of glycerokinase activity in obese hyperglycemic mice thus provides an explanation of the decreased dependence on carbohydrate metabolism in the adipose tissue of these animals. The increased concentration of glycerophosphate, due to lowered rates of conversion, may explain why the glucose uptake by the adipose tissue is decreased, even in the presence of increased insulin. The accumulation of glucose in the blood may, in turn, be the reason for the decreased release of fatty acids during fasting, under the influence of epinephrine or fat-mobilizing substance. Reaction to the hyperglycemia, in turn, could cause the hyperplasia of the beta cells of the islets of Langerhans, the increased production of insulin, and the constant increased secretion of insulin, with resultant degranulation of the islets and an increase in circulating insulin. Finally, the increased blood glucose and insulin concentrations may cause increased synthesis of glycogen and fat in the liver. This interesting syndrome (which shows many points of similarity with certain maturity-onset diabetes associated with obesity seen in man) may thus be the first identified diabetes which is, in fact, a disease of the adipose tissue.

We hope that enough facts have been given to substantiate the distinction between metabolic and regulatory obesities in the mouse. While the analysis of other metabolic obesities in the mouse has not been as thorough as that of the obese hyperglycemic syndrome, we could have drawn a similar comparison using, for example, the obesity due to ACTH-secreting pituitary tumors. Although we are not yet able to illustrate the differences between regulatory and metabolic obesities as thoroughly in man as in the mouse, there is evidence that the distinction is valid in man as well.

Applications to Man:

Quantitative Definition of Obesity

We have presented a variety of experimental evidence concerning the regulation of food intake and the causes of obesity. In examining the extent to which these observations are relevant to human obesity we might begin by mentioning the varied and somewhat contradictory means which are used to identify this condition. For many years it has been common to equate obesity with overweight, as determined by reference to one of the "height-weight" tables popularized by life insurance companies. Early tables, such as those based on the Medico-Actuarial investigations of 1912, gave average weights for given height and age, the connotation being that the average was acceptable from a health viewpoint. It was eventually realized, however, that accumulation of weight after the age of 30 is common in most industrialized countries and that this increased weight is due to an increase in adiposity which is, in turn, linked to increased mortality from degenerative disease. In 1943 the Metropolitan Life Insurance Company issued new tables which, being based on data for the younger age groups, eliminated this middle-age weight increase and, in addition, recognized the variability of the human constitution to the extent of replacing the single average weight for each height with three values for three classes of frame size. However, classification of a given individual's frame as small, medium, or large was left to the judgment of the examiner; no definitions were given.

Although an individual who is markedly overweight is quite likely to be obese, moderate levels of overweight are not necessarily indicative of excessive fat. On the basis of normative tables most linesmen of professional and collegiate football teams would be classified as overweight, even though many of them contain less fat than their lighter, nonathletic contemporaries. Dissatisfaction with this approach to the identification of obesity has led to attempts to determine body fat by a variety of methods—through multiple anthropometric measurements; estimation of total body water; body densitometry, in water or helium; measurement of krypton absorption; total-body potassium determination; measurement of skinfold thickness by means of constant-pressure calipers; and radiography of soft tissue.

Performance or observation of such methods soon reveals that, while they are important research tools, the execution of any but the skinfold determinations is too difficult and too time-consuming for the investigator who wants simply to make a rapid diagnosis of obesity, obtain a reasonably accurate estimate of its extent, and follow its changes. Fortunately, measurements of the most accessible skinfold, the triceps skinfold, have been shown to correlate remarkably well with other determinations of body fat (*53*), a finding not surprising in view of the fact that 50 percent of human body fat is situated immediately beneath the skin. Seltzer and J. Mayer (*53*) have published a set of suggested standards, based on measurements of triceps skinfold, which should be particularly useful through the growth period, when variations in *weight* are very difficult to interpret.

Hunger and Satiety in Man

Despite the historical significance and obvious importance of the sensory aspects of hunger and satiety, systematic investigation of these phenomena in man has only recently been undertaken. While much remains to be learned, a study by Monello and J. Mayer (*54*) has provided approximately 400 items of information on 800 persons, adult and adolescent, obese and nonobese. Analysis of these data revealed that a great variety of sensations are recognized as signaling hunger, and that the frequency with which they are experienced varies appreciably between age groups, between sexes, and between individuals. The timing and sequence of specific sensations appears to vary as well. Furthermore, the relationships between moods, preoccupation with thoughts of food, and degree of hunger were found to be more complex and more variable than had hitherto been recognized.

While hunger was associated with identifiable sensations which, in general, increased in number and intensity as mealtime approached, satiety —the cessation of any urge to eat— was not necessarily associated with any characteristic sensation, nor did it simply coincide with the disappearance of sensations of hunger. It was often associated, particularly in adults, with changes in mood. In growing youngsters, however, sensations of gastric fullness frequently did accompany satiety. The sensory picture is thus not inconsistent with the hypothesis that satiety is dependent on events occurring largely at a subcortical level. Comparison of the hunger and satiety pictures in obese and nonobese individuals suggested that abnormalities of satiety may be more prevalent than abnormalities of hunger.

Inactivity Is a Cause of Obesity

While below-average muscular activity on the part of the obese is a matter of popular and immemorial record, there is a physiologic basis for reassessing the possibility that inactivity plays a primary role in the etiology of their disorder. That regulation of food intake does not function equally well at all levels of energy expenditure was first demonstrated when Gasnier and A. Mayer (*2*) compared the food intake and body weights of unshaved and shaved animals exposed to various environmental temperatures. J. Mayer has since demonstrated, in both animal and human studies, that this is also true when the variation in energy expenditure is due to changes in the level of physical activity (Fig. 4). Within the range of moderate activity, rats exercised on a treadmill accurately regulate their energy expenditure and, therefore, their body weight. However, if the activity is too intense, the animals become exhausted, their food intake decreases, and their weight drops. If activity decreases below a threshold level, food intake does not continue to decrease correspondingly (*55*). In fact, at very low levels of activity, food intake increases again, a phenomenon interpreted by Christophe and Mayer (*56*) as reflecting decreased glucose utilization (and exploited by farmers who fatten animals by cooping them up). Humans subjected to these conditions respond in a similar manner. Evidence that low levels of activity lead to an energy surplus and consequent obesity is complemented by the finding that exercising genetically obese mice, which are usually extremely inactive, causes spontaneous loss of weight. This observation is valid for animals with experimentally induced obesity as well.

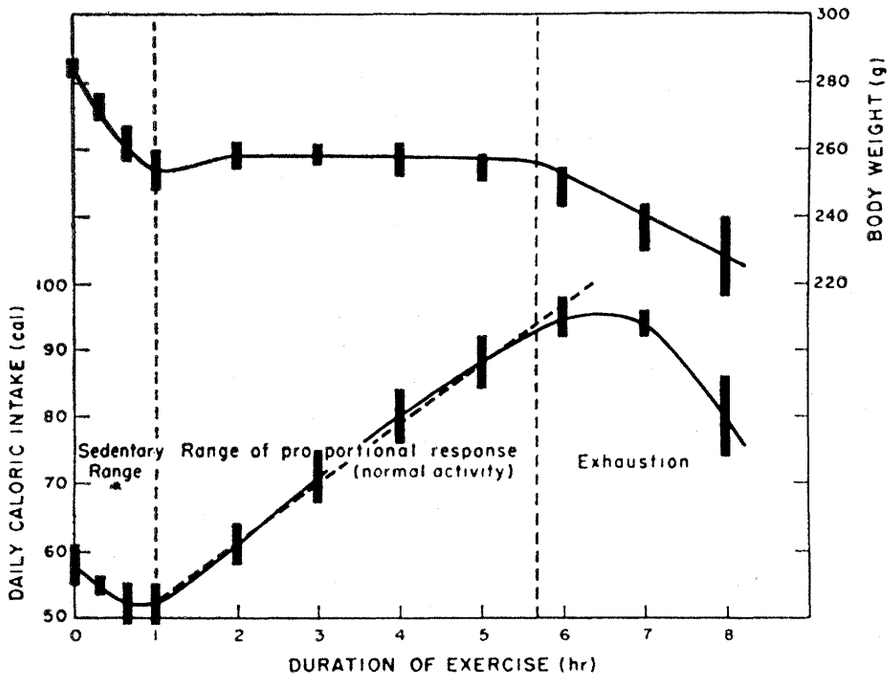

Fig. 4. Voluntary caloric intake and body weight as functions of exercise in normal rats. When rats are exercised on the treadmill for varying periods of time, food intake increases with energy expenditure only in the range of "normal activity." At very low levels of activity (sedentary range) and at very high levels of activity (exhaustion range) the response is paradoxical. This phenomenon appears to hold in all species, including man, in which it has been studied.

In recent studies of school children in the Boston area, J. Mayer and his associates have found further evidence of the etiologic significance of inactivity. Initial observations revealed that the onset of obesity among these students usually occurred during the winter, a time of relative confinement (*57*). In a more detailed study the food intakes and activity schedules of 28 obese high school girls were compared with those of an equal number of normal-weight controls, matched on the basis of height, age, school grades, and socioeconomic status. It was found that the obese girls ate less, not more, than the controls but spent a strikingly smaller amount of time (two-thirds less) in occupations involving a significant amount of exercise (*58*). Similar observations were made in comparisons of obese and nonobese boys (*59*). Increasing the physical activity of obese youngsters resulted in a decrease in body fat (*60*), as would be predicted from animal studies cited above.

By employing a technique originally developed for time and motion studies in industry, it has been possible to quantify more precisely the relative amounts of energy expended in spontaneous activity by normal and obese subjects. Motion pictures are taken for brief periods at regular intervals, then analyzed in a way which permits quantitative estimation of the subject's activity during the period of observation. This information, in conjunction with a knowledge of the subject's weight, permits computation of a reliable index of energy expenditure (*61*). With this tool it became possible to demonstrate unequivocally that, for example, the average obese adolescent girl expends far less energy during scheduled "exercise periods" than her nonobese counterpart does.

Although these and subsequent studies leave little doubt that inactivity is a major factor in children's and adolescents' obesity, the causes of this inactivity are not obvious. Certain physiologic conditions—low serum iron, for example—found more frequently in obese children than in normal children may contribute to their inactivity (*62*). However, once obesity is established, consequent psychologic traumas may act to make inactivity self-perpetuating. Monello and J. Mayer found that the responses of a large sample of obese girls to projective tests characteristically reflected such traits as "obsessive concern," "passivity," and "withdrawal," associated with "expectation of rejection" (*63*). The work of Stunkard and his associates (*64*) indicates that obesity during adolescence, when the individual's image of his adult body is developing, may have a marked effect throughout life.

Environmental and Genetic Factors in Human Obesity

The role of certain environmental and genetic factors in the development of human obesity is becoming clearer. That obesity "runs in families" has been abundantly demonstrated, by Bauer in Vienna, by Rony in Chicago, by Angel in Philadelphia, by Dunlop in Edinburgh, and more recently by J. Mayer and his associates in Boston (*65*). There is little doubt that sociocultural factors are involved. Angel noted a much greater prevalence of obesity in immigrants than in "old Americans," while a recent study conducted in Manhattan by Moore, Stunkard, and Srole (*66*) showed, particularly in women, a strong negative correlation between social class and obesity. At the same time, the importance of genetic background in obesity is indicated by a variety of evidence: evidence from the study of identical and nonidentical twins showing the much closer similarity of weights of identical twins, even if reared in different environments; evidence that segregation takes place in the transmission of obesity; demonstration that the sex ratios of children of various combinations of thin and fat parents are statistically different from the ratio for the population as a whole (*65*); demonstration that the weight of a child adopted from birth is poorly or not at all correlated with that of its foster parents, unlike the situation for a natural child (*67*). Finally, Seltzer and J. Mayer (*68*) have demonstrated that the obese differ from the nonobese in features other than the amount of fatty tissues. Obesity occurs most frequently in a physical type characterized by a skeleton which is larger than normal, a large (though generally unexercised) muscle mass, and short, broad extremities. Inasmuch as body type is known to be genetically controlled, this study also indicates the importance of genetic factors in determining susceptibility to obesity.

Conclusion

This is not the place to consider the medical significance of obesity in terms of conditions such as heart disease and hypertension, diabetes, and arthritis. These very complex interrelationships have been dealt with elsewhere (*69*). We hope that enough evidence has been presented to demonstrate that energy balance is normally maintained by a precise and reliable physiologic mechanism, and that the energy surplus represented by obesity may reflect direct failure of this mechanism or some combination from a variety of neurological, endocrine, enzymatic, and psychological disorders. Environmental conditions as well as genetic and traumatic factors may contribute to the development of obesity. If increasing mechanization brings us below the level of energy expenditure at which food intake is properly regulated, appropriate habits of exercise will have to be established and maintained.

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