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The Physiological Psychology of Hunger: A Physiological Perspective

Mark I. Friedman
University of Massachusetts

Edward M. Stricker
University of Pittsburgh

Hunger and satiety are usually discussed from the perspective of the central nervous system. In this paper we instead find the foundation for an understanding of hunger in the basic biochemical and physiological processes of energy metabolism. Such considerations suggest that the stimulus for hunger should be sought among changes that occur in the supply of metabolic fuels rather than in the utilization of specific nutrients or in the levels of fuel reserves. This line of reasoning diverts attention from the brain, which is not usually subject to dramatic fluctuations in its fuel supply, and focuses instead on the intestines, adipose tissue, and liver, the three peripheral organs that are most involved in the production or delivery of metabolic fuels. We propose that the stimulus for hunger derives from information provided to the brain by the liver in the course of normal hepatic function. More specifically, the stimulus for hunger may be associated with an alteration in oxidative metabolism within the liver, with food intake reversing that change. This view of hunger conforms closely to the fundamental features of caloric homeostasis and makes unnecessary such traditional hypothetical constructs as hunger and satiety *centers, glucostat, lipostat,* and *body weight set point.*

Physiological psychologists have traditionally viewed hunger from the perspective of the central nervous system. The early findings of Brobeck and his colleagues, that damage to specific hypothalamic areas provokes dramatic alterations in food intake and body weight (Anand & Brobeck, 1951; Brobeck, Tepperman, & Long, 1943), first riveted attention to the brain. Their concept of a ventromedial hypothalamic *satiety center,* which inhibits the activity of a primary *feeding center* in the lateral hypothalamus, provided the framework for much of the theorizing about hunger that has occurred in the last quarter of this century. Multiple physiological factors are now believed to stimulate feeding and thus to ensure the constancy of body weight, body temperature, and glucose utilization, each of which has been assumed to exert its influence on the medial or lateral hypothalamic areas or both (e.g., Anand, 1961; Epstein & Teitelbaum, 1967; Stellar, 1954; Stevenson, 1969).

We believe that preoccupation with central controls has been premature and has led to misconceptions about the stimuli for hunger, misconceptions that become apparent when experimental findings are viewed from a more contemporary physiological perspective. Accordingly, rather than accepting the dual hypothalamic model as the starting point, we sought for the foundation of an understanding of hunger in the basic biochemical and physiological processes of energy metabolism in higher mammals. We believe this approach leads to a view of hunger that conforms more closely to the fundamental features of caloric homeostasis that have been disclosed in recent years. Such a view also makes unnecessary the notion of multiple stimuli for hunger and the need for such traditional hypothetical constructs as *body weight set point, lipostat,* and *glucostat.*

The present paper is divided into three sections. First, we briefly describe energy metabolism, with an emphasis on those prin-

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Requests for reprints should be sent to Mark I. Friedman, Department of Psychology, University of Massachusetts, Amherst, Massachusetts 01002.

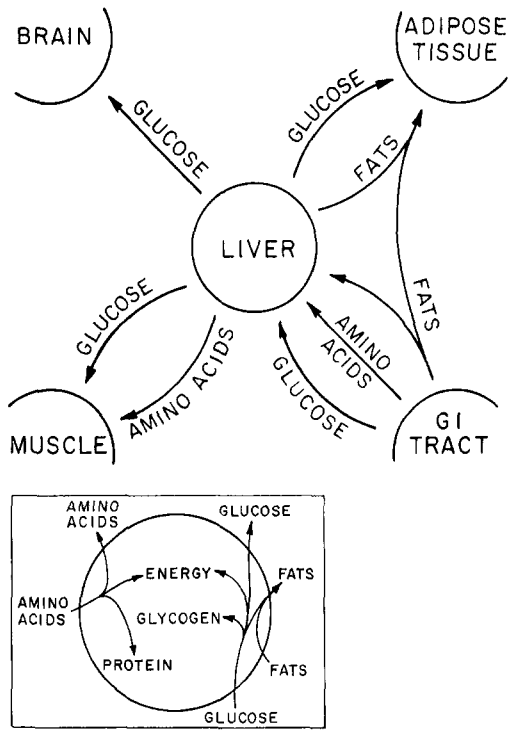

FIGURE 1. Disposal of metabolic fuels in the postprandial state. (Because the liver plays a pivotal role in determining the fate and availability of metabolic fuels, insert shows the pattern of substrate flow in that organ.)

ciples that seem most relevant to the present discussion. Then, we relate that presentation to our view of hunger, and from that perspective reexamine selected experimental findings that have provided the strongest arguments for traditional hypotheses. Finally, we reevaluate the evidence that dual hypothalamic centers control hunger and satiety and then consider the origin of the metabolic stimulus that signals the animal to feed.

ENERGY METABOLISM

Metabolism in tissues requires continuous supplies of utilizable fuels. These may be derived from carbohydrate, fat, or protein, which are ingested due to hunger or are mobilized from bodily energy reserves. The physiological and biochemical mechanisms that maintain and direct energy metabolism have been investigated extensively and are the subject of many excellent reviews (Newsholme & Start, 1973; see also Cahill, 1970; Felig, 1973; Flatt & Blackburn, 1974; Levine & Haft, 1970; Owen & Reichard, 1971a; Tepperman & Tepperman, 1970). These mechanisms can be conveniently grouped into those that provide for the initial disposal of ingested nutrients following a meal and those that permit a measured recruitment of stored fuels in the postabsorptive state. They are briefly summarized as follows.

Disposal of Metabolic Fuels

Food consumption usually delivers metabolic fuels to the animal in amounts that far exceed its immediate requirements. Because of the large capacity of the gastrointestinal tract to accommodate food, and the relatively slow absorption of nutrients therefrom, the period during which metabolic fuels are provided by feeding extends well beyond the meal itself. During this time, ingested nutrients either are utilized directly or are stored for later use (see Figure 1). Carbohydrates are broken down into utilizable sugars, such as glucose, and are absorbed from the small intestine into capillaries going directly to the liver via the hepatic portal system. Glucose freely enters the liver and is there either oxidized to provide energy, stored in limited quantities as glycogen, or converted to lipids (lipogenesis), which enter the circulation and are transported to adipose tissue for storage. The circulating glucose not removed by the liver is used for energy production in brain, muscle, and other tissues or else is stored in adipose tissue as triglycerides. Wasteful glycosuria is always avoided, regardless of how much carbohydrate is ingested, except in disease states (e.g., diabetes mellitus).

Protein from the food is degraded to amino acids which, after absorption, are either resynthesized into new protein, used for energy production (especially when they are in excess and little carbohydrate is available), or metabolized in the liver to carbohydrate or lipid. Dietary fat, mainly as triglyceride, passes from the intestine and is transported through the lymphatic system to the general circulation. The bulk of the triglyceride is hydrolyzed in the capillary beds to liberate glycerol and free fatty acids. The glycerol is converted in the liver to glucose, which is handled as

described above. The free fatty acids can enter tissues rapidly and be utilized, but usually they are esterified to reform triglycerides within adipose tissue cells and then are stored there. The storage capacity of adipose tissue is virtually limitless, and thus, lipids derived from carbohydrate, protein, or fat can always be stored when caloric intake exceeds expenditures.

Mobilization of Metabolic Fuels

The need for energy production by living cells is continual. Thus, the animal with no food to consume must consume itself. Compared to the postprandial flood of nutrients from the gastrointestinal tract, the postabsorptive mobilization of metabolic fuels from reserves (see Figure 2) is conservatively attuned to tissue needs, thereby maximizing the duration of adequate maintenance during an indeterminate period of privation. Of greatest significance is the lipid depot in adipose tissue, which normally contains at least 80–90% of the calories stored. Triglycerides in adipocytes are hydrolyzed to form glycerol and free fatty acids (lipolysis), which are then released into the blood. Both are taken up by the liver, in which glycerol is transformed into glucose and the free fatty acids are either used for energy or converted to ketone bodies (ketogenesis). Glucose is also synthesized (gluconeogenesis) from amino acids and other substrates (see below), and the reduction of liver glycogen (glycogenolysis) adds to the glucose supply. The glucose thus produced is released into the blood, and the major portion of it is used by the brain; the ketone bodies, in contrast, are used as metabolic fuels by brain as well as other tissues. Free fatty acids not taken up by the liver provide a major fuel for muscle but cannot be used by the brain.

Aside from this ebb and flow of nutrients, there are four additional features of metabolism that have important implications for our view of hunger.

1. Both endocrine and neural events help to satisfy the organism's needs for metabolic fuels. For example, two antagonistic pancreatic hormones, insulin and glucagon, provide a coordinated control over enzymes in the

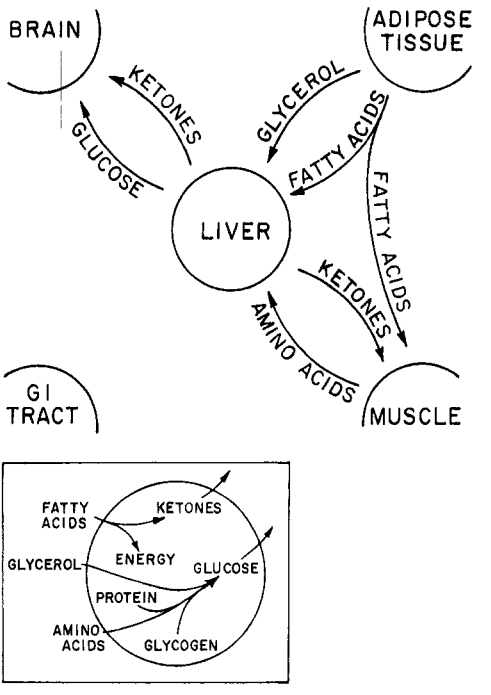

FIGURE 2. Mobilization and disposal of metabolic fuels in the postabsorptive state. (Because the liver plays a pivotal role in determining the fate and availability of metabolic fuels, insert shows the pattern of substrate flow in that organ.)

liver and adipose tissue that direct the deposition and mobilization of the different metabolic fuels (e.g., Randle et al., 1966; Unger, 1974). Thus, the postprandial delivery of glucose into the hepatic portal system, together with other meal-related events, stimulates the secretion of insulin, which promotes the formation of lipids and glycogen (while inhibiting their mobilization) as well as the uptake of glucose into muscle and its utilization there. In the postabsorptive period, on the other hand, insulin secretion declines and glucagon secretion increases; these changes promote the mobilization of liver glycogen and fats from storage and the production of new glucose from glucogenic precursors (Cahill et al., 1966; Marliss, Aoki, Unger, Soeldner, & Cahill, 1970). Some of these metabolic effects are additionally stimulated by growth hormone and by adrenal glucocorticoids and catecholamines, secretions of which increase during fasting (e.g., Exton, 1972; Jeanrenaud, 1968). Complementing

them still further (and, in part, modulating all of the endocrine secretions) are the actions of the autonomic nervous system. Thus, excitation of the sympathetic nerves stimulates glycogenolysis in the liver (Shimazu & Fukuda, 1965) and lipolysis in adipose tissues (Havel & Goldfien, 1959), whereas converse effects in the liver result from activation of the parasympathetic fibers (Shimazu, 1967).

2. The supply of fuels to the brain is elaborately defended even during prolonged fasting. Insulin is not required for transporting glucose into nerve cells, and thus glucose utilization by the brain continues early in the postabsorptive state despite reduced insulin secretion. In contrast, utilization of glucose by muscle is diminished when insulin levels are reduced, and glucose is thereby spared for use by the brain (Cahill et al., 1966). Further conservation of glucose results from the utilization of free fatty acids and ketone bodies by muscle, since intermediates in their metabolism retard the degradation of glucose into pyruvate (glycolysis) and its subsequent oxidation in the tricarboxylic acid cycle (Randle, Garland, Hales, & Newsholme, 1963). Moreover, the pyruvate and lactate formed from glucose in nonneural tissues are returned to the liver for resynthesis into glucose to be used by the brain (Owen, Felig, Morgan, Wahren, & Cahill, 1969). Because liver glycogen stores are relatively small, these processes are important for conserving glucose and thereby minimizing the need for gluconeogenesis from amino acid substrates (principally alanine) produced by muscle catabolism (Felig, Owen, Wahren, & Cahill, 1969). Nevertheless, as fasting continues, the production of glucose decreases, thus conserving body protein, and ketone bodies provide increasingly more of the substrate that is used for metabolic fuel by the brain (Owen et al., 1969; Sherwin, Hendler, & Felig, 1975). For example, it is estimated that more than 60% of brain oxygen consumption in obese human subjects during prolonged starvation is provided by the oxidation of ketone bodies (Owen et al., 1967). At this time, the utilization of ketone bodies by muscle diminishes, and free fatty acids are preferentially oxidized, thus sparing the ketone bodies for metabolism by the central nervous system (Owen & Reichard, 1971b). Such alterations in the mixture of glucose and ketone bodies that is delivered to the brain permit it to maintain its function without disruption (see also Krebs, Williamson, Bates, Page, & Hawkins, 1971; Sokoloff, 1973).

3. Lipid deposition and mobilization are directly related to the content of triglycerides already present in adipose tissue, in addition to being influenced by hormones (especially insulin) and autonomic tone. Thus, decreases in tissue lipid levels shift equilibrium conditions toward fat storage, whereas increases in lipid levels tend to facilitate fat loss. This feature of adipose tissue metabolism underlies observations that postprandial glucose uptake and lipogenesis are greater in a previously fasted animal, whose adipocytes have been partially emptied, than in an animal eating ad libitum (Connor & Newberne, 1974; Tepperman & Tepperman, 1958), whereas the basal rate of lipolysis is greater in obese subjects than in lean individuals (Goldrick & McLoughlin, 1970; Hartman, Cohen, Richane, & Hsu, 1971). The intrinsic tendency toward maintenance of lipid mass in adipose tissue might also provide the basis for apparent alterations in the sensitivity of adipose tissue to insulin as a function of body weight (Di Girolamo & Rudman, 1968; Salans, Knittle, & Hirsch, 1968), as well as for the long-term stability of body weight at fairly steady levels presumably set by genetic and early postnatal factors (Johnson, Stern, Greenwood, Zucker, & Hirsch, 1973; Knittle & Hirsch, 1968), which is commonly observed in adult animals.

4. The liver is not entirely dependent on activity in the tricarboxylic acid cycle for energy production. In the fed state, glucose is usually the primary substrate in nonruminants, and its oxidation to CO_2 is the major source of energy in the liver, as in all tissues. In contrast, whereas peripheral tissues mainly oxidize free fatty acids and ketone bodies rather than glucose during fasting, the liver uniquely lacks the enzyme needed to convert the ketone bodies synthesized there into a substrate that can be oxidized in the tricarboxylic acid cycle (Krebs et al., 1971). Instead, the partial oxidation of free fatty acids that occurs in ketogenesis may provide

a considerable portion of the energy that is produced (Krebs & Hems, 1970; Mayes & Felts, 1967; Wieland, 1968).

To summarize, energy metabolism is maintained by alternating tides of nutrients that sweep in from the intestines or adipose tissue at regular intervals depending on when food consumption occurs. Adipose tissue participates actively in metabolism by removing the excess nutrients that are usually obtained during each meal and by releasing them in the subsequent postabsorptive period. This tissue thus provides a massive energy buffer that prevents dramatic shifts in nutrient supply despite the episodic nature and inconstant magnitude of food ingestion. The liver complements the function of adipose tissue and ensures that nutrient supplies are sufficient and appropriate to the specific needs of individual tissues. In satisfying those needs, metabolic fuels are used interchangeably in peripheral cells, while the brain's special requirements for glucose and ketone bodies are accommodated by the economic utilization of these fuels by nonneural tissue. This harmony of tissue metabolisms is orchestrated by neural and endocrine actions, which influence the course of bidirectional biochemical reactions both by establishing substrate availability and by modifying enzyme activities. These integrated physiological events, unaccountably neglected in most essays on hunger (see discussion of a "bodiless psychology" by Le Magnen, 1971), provide the background for our present formulation.

Hunger

Traditional interpretations given for the appearance of hunger are that food intake serves (a) to replete diminished fat reserves (Kennedy, 1953) and (b) to increase the utilization of glucose (Mayer, 1955). We believe that hunger instead occurs whenever the immediate availability of utilizable metabolic fuels is reduced below some critical level (e.g., as might occur early in the postabsorptive state). In essence, our arguments rest on two basic observations regarding energy metabolism. The first is the fact that the supply of metabolic fuels to all tissues always remains adequate for them to function during physiological conditions and even during prolonged food deprivation (until, of course, the starving animal is in extremis). The second is the fact that, with but a few exceptions, each of the various metabolic fuels is equally capable of providing energy in all tissues. From the perspective of these phenomena, it seems reasonable to focus on caloric homeostasis, rather than the maintenance of energy stores, as the goal of feeding behavior and the complementary biochemical and physiological mechanisms that serve to maintain the fuel supply. Moreover, it does not seem likely that quantitative changes in the utilization of specific nutrients would provide a stimulus for hunger, because compensatory changes in the utilization of other nutrients would limit their functional significance. Instead, we propose that the stimulus for hunger should be sought among changes that occur in the supply of metabolic fuels. This line of reasoning diverts attention from the brain, which is not usually subject to dramatic fluctuations in its fuel supply, and focuses instead on the intestines, adipose tissue, and liver, the three peripheral organs that are most involved in the production or delivery of metabolic fuels.

In this section we shall reevaluate familiar research from a perspective that focuses on the availability of utilizable fuels during various experimental conditions and emphasizes the changes in fuel supply that can result from variations in diet, in tissue demands, and in storage or mobilization of nutrients. We have organized our discussion around experiments related to the lipostatic and glucostatic hypothesis, since these have provided the focus for most of the research on hunger during the past 25 years.[1]

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[1] A third familiar proposal is the "thermostatic hypothesis" of Brobeck (1948) which, stated simply, holds that "animals eat to keep warm." At the time it was formulated, this hypothesis rested largely on the incontrovertible facts that (a) food intake is adjusted in accordance with changes of energy balance (i.e., it typically increases in cold environments and decreases in warm environments), (b) meal size could be influenced by the heat liberated during the assimilation of the ingested nutrients, and (c) the hypothalamus was involved in the controls of both food intake and body temperature. Mechanisms

Lipostatic Hypothesis

As animals mature, their progressive increase in body weight reflects growth in a variety of tissues, including bone, muscle, and organs. In the adult animal, however, such structures stop growing rapidly, and changes in body weight result mostly from changes in the mass of adipose tissue due to energy imbalances. Thus, increases in body weight that occur when caloric intake exceeds expenditures can be attributed primarily to storage of the extra calories as fat (obesity), whereas decreases in body weight when expenditures exceed intake reflect the mobilization and utilization of body fat. As might be expected, little change in body weight occurs, even when food intake is unusually high, when caloric expenditures are also elevated, as in exercise, lactation, or the need for thermogenesis (e.g., Brobeck, 1948; Kennedy, 1953, 1961; Mayer, 1955).

An increased utilization of calories resulting in the production of heat following overfeeding, and a decreased utilization during fasting, serve to minimize the consequences of fluctuating volumes of food intake (e.g., Adolph, 1947; Lyon, Dowling, & Fenton, 1953; Sims, Horton, & Salans, 1971). Because these changes may not be entirely adequate to this task (viz., metabolism does not stop during food deprivation), changes in food intake usually provide a major contribution to the maintenance of energy balance. For example, when rats are made obese by forced hyperalimentation or by excessive voluntary feeding induced either by injections of insulin or by electrical brain stimulation, they reduce their consumption of food when the respective treatment is terminated and remain hypophagic until their body weights return to normal (Cohn & Joseph, 1962; Hoebel & Teitelbaum, 1966; Steffens, 1975). Similarly, rats that have been starved increase their food intakes and remain hyperphagic until body weight losses have been restored (Kennedy, 1950). According to the lipostatic hypothesis, the increased body-fat reserves resulting from the former treatments provide the brain with a blood-borne signal for satiety that results in decreased feeding, whereas the depleted fat reserves resulting from the latter treatment lead to a reduction of that stimulus and, in consequence, increased feeding. In both cases, it is believed that food intake is adjusted appropriately so as to regulate body-fat reserves around some predetermined "set point" (Kennedy, 1953; Mayer, 1955).

As mentioned previously, we believe that maintenance of body-fat stores is not the goal of food intake but may instead reflect an intrinsic tendency toward stability of lipid levels in adipose tissue, and that observed variations in food intake result from changes in the supply of metabolic fuels. Thus, the animal made obese may decrease its feeding not because of some signal for satiety but because of the absence of a stimulus for hunger, due to the considerable nourishment that is provided by the presumably heightened availability of free fatty acids (Björntorp, Bergman, & Varnauskas, 1969; Issekutz, Bortz, Miller, & Paul, 1967; see also Le Magnen, Devos, Gaudilliere, Louis-Sylvestre, & Tallon, 1973). Similarly, the previously fasted animal may increase its feeding not because it receives less of a satiety signal but because enhanced lipogenesis after a meal more rapidly reduces the normal postprandial availability of nutrients in the circulation (cf. Brobeck, 1975). According to this conceptualization, we would expect inhibition of lipolysis to prevent the decline in food intake that occurs when any of the above treatments producing obesity are terminated, whereas inhibition of lipogenesis should reduce food intake in previously fasted animals. Evidence consistent with both hypotheses has been reported recently (Le Magnen & Devos, 1970; Sullivan & Triscari, 1976).

These same considerations are relevant to an analysis of the periodic meals taken by

for thermoregulation and for the regulation of caloric homeostasis are more easily distinguished now, as are neural controls within the hypothalamus. In addition, subsequent investigations have shown that food consumption is not correlated with fluctuations of temperature in the brain (Rampone & Shirasu, 1964). Furthermore, in a particularly illuminating study, Rozin and Mayer (1961) found that food intake by fish was depressed reliably by a decrease in ambient temperature. These results would be expected if feeding was responsive to the need for metabolic fuels rather than to changes in body temperature per se.

rats feeding ad libitum. The patterning of meals has been studied extensively by Le Magnen and his colleagues, who discovered that meal size is not dependent on the length of time since the preceding meal but that it does predict the interval until the onset of the next meal (Le Magnen & Tallon, 1966). These important findings suggest that feeding is not initiated in order to replace metabolic expenditures and therefore that meal size may be strongly influenced by nonmetabolic factors. Ingestion of food thus provides an inconstant quantuum of calories, and hunger seems to recur only after those calories have been expended. For example, meal frequency is not nearly so great by day, when free fatty acids are available due to lipolysis, as at night, when fat is stored (Le Magnen et al., 1973).

Perhaps the strongest arguments in support of the lipostatic hypothesis have been based on the hyperphagia and obesity that result following ventromedial hypothalamic (VMH) lesions. Animals with such lesions usually eat voraciously for weeks but eventually reduce food intake and stabilize body weight at a new, elevated level (Brobeck, 1946; Hetherington & Ranson, 1940; Kennedy, 1950). Their obesity seems to be as well defended as normal body weight is in neurologically intact animals, since even after being deprived of food and thereby forced to lose weight, these brain-damaged rats quickly reattain their previous level of obesity when given ad libitum access to food (Brobeck et al., 1943). Furthermore, VMH lesions do not induce hyperphagia in rats that have previously been made obese by chronic insulin treatments, but they do prevent the loss of body weight that otherwise would occur when the injections of insulin are ended (Hoebel & Teitelbaum, 1966).

In interpretations of these findings, the controls of feeding have been linked to the regulation of body fat in two ways. First, it has been proposed that VMH lesions release a primary "hunger center" from normal inhibitory influences (Brobeck, 1955; Hervey, 1959; Teitelbaum, 1961). According to this hypothesis, VMH lesions induce hyperphagia because satiety signals arising from body fat are insufficient to activate the residual VMH neurons, and thereby to suppress feeding, until the animal becomes obese. Alternatively, it has been proposed that the function of the ventromedial hypothalamus is to stabilize fat stores and that VMH lesions raise the "set point" at which body fat is regulated (Keesey & Powley, 1975; Kennedy, 1953). According to this hypothesis, the hyperphagia seen after VMH lesions is an appropriate, well-controlled response designed to achieve a higher level of regulated body fat.

We believe that in neither of these interpretations is the VMH syndrome viewed from the correct perspective. Rather than adipose tissue passively accommodating the extra food that is consumed due to a primary disturbance in the hypothalamic controls of feeding, considerable evidence indicates that VMH lesions produce a primary disruption in fat metabolism in favor of lipogenesis, with secondary consequences for feeding. For example, in vivo and in vitro studies have shown that rats with VMH lesions incorporate more glucose as fat, burn less fatty acids, and mobilize less fat from adipose tissue than neurologically intact control rats (e.g., Frohman, Goldman, & Bernardis, 1972; Goldman, Schnatz, Bernardis, & Frohman, 1970, 1972a; Haessler & Crawford, 1967). This increased accumulation of fat has been demonstrated to occur as early as 12 to 48 hours after VMH lesions,[2] even when food is withheld or restricted, with the degree of lipogenesis correlating highly with the hyperphagia observed when the animals are subsequently allowed to feed ad libitum (Hustvedt & Løvø, 1973; Løvø & Hustvedt, 1973; see also Hustvedt & Løvø, 1972). Thus, an animal with VMH lesions may not increase its food intake *in order to* gain weight but because it *is* gaining weight. That is, animals may become hyperphagic after VMH lesions because more of the ingested food is removed from the circulation to be deposited as fat than previously (see

[2] Presumably, alterations in metabolism begin immediately after VMH lesions, thereby contributing to the ravenous feeding that is often reported as the anesthesia dissipates (see also Rabin, 1968; Reynolds, 1963) as well as accounting for the augmented intakes that occur following local anesthetization of the ventromedial hypothalamus (Epstein, 1960).

Han, 1967; Han & Frohman, 1970), and because these expanding fat stores are also less accessible.

Since lipogenesis is well-developed at night in the intact rat, the primary metabolic effect of the VMH lesions is to enhance fat deposition by day. Instead, these lesions eliminate daytime lipolysis in rats despite excessive eating during the previous dark period, and glucose clearance rises to high rates throughout the 24-hour period (Le Magnen et al., 1973). The diminished availability of free fatty acids by day is presumably responsible for the increased food intake that occurs then, and that increase amounts for most of the hyperphagia that is observed in rats after VMH lesions (Balagura & Devenport, 1970; Brooks, Lockwood, & Wiggins, 1946; Le Magnen et al., 1973). Thus, we would expect treatments that either interfere with fat storage or promote lipolysis to limit hyperphagia following VMH lesions (cf. Kennedy, 1953).

The physiological changes that follow VMH lesions result, in part, from the well-documented increases in circulating insulin levels; in addition, the normal modulatory action of growth hormone on hyperinsulinism is prevented because secretion of that hormone is impaired (e.g., Frohman & Bernardis, 1968; Steffens, 1970). However, since increased lipogenesis occurs despite replacement of growth hormone or elimination of hyperinsulinemia (Goldman et al., 1970, 1972b; see also Friedman, 1972; Vilberg and Beatty, 1975), it seems that alterations in the neural controls of glucose and fat metabolisms must parallel the endocrine effects. The net result is an increased deposition of fuels that is so pronounced that gluconeogenesis, normally seen only during fasting, is found after brain damage despite hyperphagia (Holm, Hustvedt, & Løvø, 1973; see also Goldman & Bernardis, 1975). Presumably, these metabolic dysfunctions continue until a new equilibrium between lipogenesis and lipolysis is attained that permits some mobilization of the fat reserves and consequent stabilization of body weight (Martin & Lamprey, 1974).

Genetic defects in adipose-tissue metabolism of neurologically intact animals lead to alterations in food intake and body weight that are comparable to those observed after VMH lesions (although the two conditions differ in some respects; see Haessler & Crawford, 1965; Mayer, 1957; Opsahl & Powley, 1974). For example, abnormal lipogenesis occurs in at least two strains of rodents, the *obob* mouse and the *faja* rat, even when food intake is restricted (Alonso & Maren, 1955; Bates, Mayer, & Nauss, 1955; York & Bray, 1973; Zucker, 1975). This primary metabolic dysfunction enhances the postabsorptive removal of utilizable fuels from the circulation and presumably is responsible for the increases in food intake and body fat that develop. The seasonal obesity of animals prior to migration or hibernation (Farner, Oksche, Kamemoto, King, & Cheyney, 1961; Klain & Rogers, 1970; see also Mrosovsky, 1974), and the daily accumulation of fat in small birds that precedes nocturnal inactivity (Kendeigh, Kontogiannis, Mazac, & Roth, 1969; Wolf & Hainsworth, in press), may promote hyperphagia for similar reasons.

In addition to the changes in fat metabolism, a more rapid rate of gastrointestinal clearance may reduce the duration of postprandial satiation in VMH-lesioned rats. In this respect, as in the others, rats with VMH lesions would then resemble unlesioned animals given ad libitum access to food after an imposed fast (Booth, Toates, & Platt, 1976). Nevertheless, it is well known that rats with VMH lesions do not always behave like hungry rats. For example, although rats usually are hyperphagic soon after VMH lesions, they may not work hard for food reinforcements (McGinty, Epstein, & Teitelbaum, 1965; Miller, Bailey, & Stevenson, 1950; Singh, 1973; Teitelbaum, 1957), they may become hypophagic or refuse a less palatable diet that is accepted readily by intact rats (Kennedy, 1950; Singh, 1974; Teitelbaum, 1955), and they may not eat much following vagotomy (Powley & Opsahl, 1974). We believe that changes in sensory reactivity and emotionality caused by the brain damage depressed the feeding behavior and food-directed activities in each of the experiments cited above and thereby obscured the increased incidence of hunger that resulted from concurrent metabolic dysfunctions. Indeed, there is consider-

able evidence that after VMH lesions, rats become hyper-reactive and generally unwilling to tolerate aversive experiences (e.g., Grossman, 1966; Lewinska & Romaniuk, 1966; Marshall, 1975).

In summary, excessive deposition and sequestration of metabolic fuels appears to underlie the observed hyperphagia in rats following a fast or lesions of the ventromedial hypothalamus. The fact that hunger occurs in rats with VMH lesions despite the presence of an internal excess of metabolic fuels suggests that the size of the fat depots becomes important to feeding only if the animal has ready access to them. These and other considerations dispute the traditional lipostatic hypothesis by suggesting that body-fat stores influence feeding only indirectly, through an alteration in the immediate supply of utilizable metabolic fuels that results from changes in lipogenesis and lipolysis.

Glucostatic Hypothesis

When peripheral models of hunger emphasizing gastric fill were abandoned early in this century, attention was directed instead to chemical changes in the blood that might stimulate feeding behavior. One enduring theory focused on glucose as the major metabolic fuel and initially held that small decreases in blood sugar increased food intake and that satiety resulted when blood sugar levels were restored to normal (Carlson, 1916). The simple, negative-feedback control of hunger inherent in this "glucostatic" hypothesis was strongly supported by experimental observations that insulin treatments producing hypoglycemia promoted feeding in rats (MacKay, Callaway, & Barnes, 1940) and induced hunger sensations in human subjects (Janowitz & Ivy, 1949). Indeed, the ingestion of food in response to hypoglycemia was perceived as another striking example of the way in which appetites were appropriately directed to relieve specific nutritional deficiencies (Richter, 1942a, 1942b).

Because hyperphagia is associated with hyperglycemia during diabetes mellitus, Mayer (1952) later proposed that hunger was due to a reduction in the utilization of glucose rather than to a reduction in its concentration in the blood. He further suggested that the central receptors monitoring fluctuations in glucose utilization required insulin for glucose transport (Mayer, 1955; see also Panksepp, 1974), like peripheral tissue but unlike the rest of the brain. Thus modified, the need for glucostasis has been widely accepted as an important factor in the control of food intake. This need is believed to arise from the presumed dependence of the brain on glucose for its function and is reflected in intermittent feeding episodes both because glucose stores are not appreciable and because they are disproportionately depleted between meals.

Mayer believed that the glucoreceptors were located in the ventromedial hypothalamus, since destruction of this area and hyperphagia resulted in mice that were administered goldthioglucose but not other goldthio- compounds (Mayer & Marshall, 1956). More persuasive evidence in support of this hypothesis was provided by Debons and his colleagues, who showed that goldthioglucose did not produce brain damage in diabetic mice or in mice pretreated with anti-insulin serum but that brain damage did occur in these animals when insulin was administered directly into the hypothalamus (Debons, Krimsky, & From, 1970; Debons, Krimsky, Likuski, From, & Cloutier, 1968). However, other experiments have revealed that (a) the brain damage caused by goldthioglucose results from ischemia following the local destruction of cerebral capillaries (Arees, Veltman, & Mayer, 1969), (b) similar hypothalamic damage, hyperphagia, and obesity can be produced by vascular poisons not containing glucose (Caffyn, 1972; Rutman, Lewis, & Bloomer, 1966), and (c) insulin-induced hypoglycemia promotes feeding even in animals with lesions of the ventromedial hypothalamus (Epstein & Teitelbaum, 1967). These observations raise serious doubts about the role of cerebral glucoreceptors in the control of food intake (see also Epstein, Nicolaidis, & Miselis, 1975) and reopen the question of why animals with diabetes mellitus or insulin-induced hypoglycemia show increased feeding.

In many respects, diabetes mellitus resembles starvation. That is, the familiar increase in circulating glucose levels results more from a marked increase in gluconeogenesis

than from decreased glycolysis, and increased lipolysis and ketogenesis are evident as well (Havel, 1972). While the abundance of glucose provides the brain with more than enough fuel, the periphery must depend on fatty acids and ketone bodies for metabolism, since neither of these substrates require insulin for transport into cells. However, lipid reserves are rapidly diminished in the absence of insulin (Winegrad, 1965), and consequently, ingested fats become an increasingly important source of fuel to the diabetic animal. From this perspective, the fat content of the usual laboratory diet can be viewed as "diluted" with carbohydrate, material of little metabolic significance during diabetes. The hyperphagia of diabetic animals thus resembles the increased feeding that occurs in intact rats when food is diluted with nonnutritive bulk (Adolph, 1947) and may result because the decrease in utilizable metabolic fuels in the diet reduces the diet's capacity to satiate the animal (cf. Booth, 1972b, 1972e; de Castro & Balagura, 1975). Consistent with this interpretation is the finding that diabetic animals maintained on a high-fat diet do not display hyperphagia despite continued impairments in glucose utilization (Friedman, 1975; Janes & Prosser, 1947; Richter & Schmidt, 1941).

The hyperphagia induced by insulin may similarly be traced to a decrease in all utilizable fuels, but here both peripheral tissue and brain tissue suffer. It should be noted that in addition to its well known effect on blood glucose, insulin also tends to suppress fatty acid catabolism, thereby minimizing ketogenesis and the possible substitution of ketone bodies for glucose as a metabolic fuel. Because insulin also retards glycogenolysis and gluconeogenesis, the hormone is particularly effective in lowering the circulating levels of metabolic fuels. Thus denied ready access to endogenous stores, the insulin-treated animal (not unlike the rat with VMH lesions) can only support metabolism by feeding and thereby increasing the delivery of fuels from the intestines.

The effects of insulin on cerebral glycolysis are usually emphasized (Smith & Epstein, 1969; Steffens, 1969a), because hunger does not appear unless blood sugar is depressed well below the level (70 mg/100 ml) at which glucose transport mechanisms in the brain are saturated (Crone, 1965; Daniel, Love, & Pratt, 1975). However, together with N. Rowland and C. Saller, we have recently observed that intravenous administration of ketone bodies to insulin-treated rats abolishes the adrenal sympathetic response otherwise prominent during severe hypoglycemia (see also Drenick, Alvarez, Tamasi, & Brickman, 1972; Flatt, Blackburn, Randers, & Stanbury, 1974) but does not depress feeding. Although energy metabolism in the brain is evidently restored by this infusion, the feeding behavior may have persisted due to decreased metabolism in the liver, the one organ that cannot utilize ketone bodies (see below). Consistent with this hypothesis are our additional findings that circulating catecholamines remain elevated but increased feeding behavior is prevented in insulin-treated hypoglycemic rats following intravenous infusions of fructose, a hexose that does not cross the blood–brain barrier but is readily utilized by the liver (Friedman, Rowland, Saller, & Stricker, Note 1; see also Hetenyi, 1972; Maddock, Hawkins, & Holmes, 1939). Thus, the hypothesis that insulin-induced feeding is stimulated by cerebral cytoglucopenia appears to mistakenly identify both the critical stimulus and its source.

Administration of 2-deoxy-D-glucose (2-DG) is frequently used as an alternative means of producing cytoglucopenia and hunger. This sugar inhibits glycolysis by competing with glucose as a substrate both for transport into cells and for subsequent phosphorylation but is not itself further metabolized (Horton, Meldrum, & Bachelard, 1973; Wick, Drury, Nakada, & Wolfe, 1957). In addition, 2-DG inhibits the secretion of insulin (Frohman, Müller, & Cocchi, 1973; Smith, Gibbs, Strohmayer, Root, & Stokes, 1973), which further retards peripheral utilization of glucose. As a result of these inhibitory actions, glucose utilization is decreased both in peripheral and brain tissue (Meldrum & Horton, 1973; Wick, Drury, & Morita, 1955), as occurs in insulin-treated rats; furthermore, as in diabetics, hyperglycemia and hunger coexist (Smith & Epstein, 1969). However, in contrast to either of these conditions, in-

creased food intake can do little to overcome the cytoglucopenia caused by 2-DG. In this regard, note that oxygen consumption decreases markedly after 2-DG treatment (Nicolaidis, Epstein, & Le Magnen, 1972) despite the increased production of glucose in the liver (Brodows, Pi-Sunyer, & Campbell, 1975; Hökfelt & Bydgeman, 1961).

The basis for hunger following systemic 2-DG treatment has not yet been specified. Intraportal injections of 2-DG have been shown to increase feeding (Hernandez, MacKenzie, & Hoebel, 1976; Novin, VanderWeele, & Rezek, 1973; Rowland & Nicolaidis, 1974), thus suggesting that a decrease in hepatic metabolism may provide the stimulus for hunger (see below). However, because administration of 2-DG into the cerebral ventricles also elicits feeding behavior in rats (Miselis & Epstein, 1975), central receptors may additionally participate in mediating the feeding response to systemic 2-DG treatment. If so, other studies demonstrating that alternative metabolic fuels can suppress the physiological responses that occur during cerebral cytoglucopenia (Fiorentini & Müller, 1975; Flatt et al., 1974; Hetenyi, 1972; Friedman et al., Note 1) suggest that feeding probably does not result from a decrease in glucose utilization per se.

The stimulation of hunger following treatment with substantial doses of insulin or 2-DG is disrupted by lateral hypothalamic (LH) lesions (Epstein & Teitelbaum, 1967; Wayner, Cott, Millner, & Tartaglione, 1971), even though rats with such brain damage maintain body weight by ad libitum feeding. It is also known that rats with LH lesions increase their food intake when placed in a cold environment (Epstein & Teitelbaum, 1967; see also Marshall & Teitelbaum, 1973; Zigmond & Stricker, 1972). These two findings have had an important influence on theories of hunger by suggesting that separate glucoregulatory and thermoregulatory controls of feeding exist. However, in collaboration with M. Zigmond, we have recently found that rats with LH lesions, whose food intake did not increase in response to 2-DG or large doses of insulin, did become hyperphagic when given repeated low doses of long-acting protamine zinc insulin. Furthermore, although these rats increased their food intakes when exposed to an ambient temperature of 5 °C, they failed to eat when the cold stress was made more severe by shaving off their fur prior to testing (Stricker, Friedman, & Zigmond, 1975). These results do not support the concept of multiple stimuli for hunger; instead, they suggest that the permanent feeding deficits of rats with LH lesions simply reflect their inability to behave appropriately when the homeostatic imbalance is marked and abrupt (see also Stricker, 1976).

To summarize, we believe that glucostasis is not the specific goal of feeding behavior. While it is true that several different conditions of cytoglucopenia can lead to increased feeding, it does not seem to be the decrease in glucose utilization per se that elicits hunger but, rather, a general decrease in the utilization of all metabolic fuels for energy production. Thus, food intake can be decreased in cytoglucopenic rats following the restoration of metabolism by substrates other than glucose. Recent studies of rats with goldthioglucose-induced lesions of the VMH area or electrolytic lesions of the LH area have removed the other major props for the glucostatic hypothesis, and consequently, it appears that there is now little basis for maintaining that fluctuations in glucose utilization in the brain provide the signal for the short-term control of food intake.

Implications of the Physiological Perspective

Thus far, we have reexamined a number of experimental findings from a perspective that takes into account well-known physiological mechanisms that maintain the supply of metabolic fuels. In each case we believe the data can be interpreted readily if one assumes that an alteration in the supply of utilizable fuels provides the stimulus for hunger. This theory is much more simple than contemporary notions of hunger, which we believe have been overburdened by such unsubstantiated hypothetical constructs as *lipostat, glucostat, body weight set point,* and the like. However, in abandoning these traditional concepts in favor of a more tangible physiological model, we recognize that two

basic questions still remain to be answered. First, given our perspective, what is the status of the dual hypothalamic model for the control of feeding? And second, in the absence of lipostatic and glucostatic receptors, what is the origin of the stimulus that signals the animal to feed? We shall now consider each of these general issues in turn.

Central Controls of Hunger

The ventromedial hypothalamus was first viewed as a satiety center whose function was to suppress the activity of a primary feeding center in the adjacent lateral hypothalamic area. Thus, VMH lesions were believed to increase food intake by attenuating the satiety-inducing effects of feeding (Brobeck, 1955; Miller et al., 1950), whereas LH lesions were thought to abolish ingestive behaviors by eliminating the signal for hunger (Anand & Brobeck, 1951; Stellar, 1954). A more recent view of these dual control mechanisms has them interacting to determine body weight set point. According to this model, VMH lesions raise the body weight set point, and hyperphagia results so that the animal will reestablish weight regulation, albeit at a new and elevated level; conversely, LH lesions are believed to lower the set point, and aphagia results so that the animal, perceiving its sudden "obesity," will reduce its weight to the new desired level (Keesey & Powley, 1975).

It is difficult to reconcile the proposal that VMH lesions disrupt satiety mechanisms with subsequent findings that when brain-damaged rats feed ad libitum, the intermeal interval is decreased but remains proportional to the size of the preceding meal (Le Magnen et al., 1973; Thomas & Mayer, 1968). It is also difficult to accept the hypothesis that hyperphagia occurs after VMH lesions in order to elevate fat reserves, since as discussed previously, the change in fat metabolism toward lipogenesis may precede the increase in food intake and even predict its magnitude (Hustvedt & Løvø, 1973). To describe the complex changes that increase the deposition and storage of metabolic fuels as an increase in body weight set point seems to obscure the details of the phenomenon unnecessarily, to attribute set point properties prematurely to the maintenance of fat reserves, and to mistakenly identify the cause of the hyperphagia as its consequence.

Damage in several brain areas other than the ventromedial hypothalamus has recently been reported to induce hyperphagia, but as with VMH lesions, in no instance is it clear that the increased food intake is the primary effect. Thus, feeding is increased (a) following parasagittal knife cuts lateral to the ventromedial hypothalamus (Albert & Storlien, 1969; Gold, 1970; Sclafani & Grossman, 1969)—but hyperinsulinemia results in these animals even when food is restricted (Tannenbaum, Paxinos, & Bindra, 1974); (b) following lesions of the ventral diencephalon presumed to specifically interrupt noradrenergic fibers ascending to the hypothalamus (Ahlskog & Hoebel, 1973; Ahlskog, Randall, & Hoebel, 1975)—but this hyperphagia is abolished by hypophysectomy (Ahlskog, Hoebel, & Breisch, 1974); and (c) following destruction of central serotonin-containing neurons (Saller & Stricker, 1976; see also Breisch, Zemlan, & Hoebel, 1976)—but rats lesioned when juvenile continue to grow in size as adults and show no remarkable accumulation of abdominal fat despite their elevated body weights. Thus, it seems likely that in each of these preparations hyperphagia is associated with, and possibly secondary to, some disruption in peripheral metabolism.

In the absence of data demonstrating the existence of a central system that specifically mediates satiety, the possibility arises that satiation originates in the periphery. For example, it has recently been proposed that intestinal glucoreceptors or hormones provide signals forecasting satiation (Davis, Campbell, Gallagher, & Zurakov, 1971; Novin, Sanderson, & VanderWeele, 1974). However, the involvement of pancreatic hormones in mediating these effects has not yet been excluded (see Footnote 3, below). More recently, cholecystokinin has been reported to suppress feeding in hungry rats (Smith & Gibbs, 1976), but it is still uncertain whether the doses used fall within the physiological range. Alternatively, satiation may result from removal of a peripheral metabolic stimulus that activates feeding, both due to conditioned effects of food consumption (Booth,

1972a; Louis-Sylvestre, 1976; Stunkard, 1975) and to unconditioned physiological changes that result from the ingestion and rapid absorption of carbohydrates (Pilcher, Jarman, & Booth, 1974; Steffens, 1969b; Strubbe & Steffens, 1975; Wiepkema, Alingh Prins, & Steffens, 1972; see below). Indeed, Booth and his colleagues have successfully simulated meal patterns of intact and brain-damaged rats with a computer model that consists essentially of a single-loop, negative-feedback system, with a diminished fuel supply from the intestines and adipose tissue in the face of ongoing energy consumption as the sole stimulus for hunger (Booth & Toates, 1974; Booth et al., 1976; Toates & Booth, 1974). Those remarkable findings obviously are in accord both with the possibility of peripheral controls for hunger and satiety and with the theoretical approach we have taken in this paper.

The role of the lateral hypothalamus as a feeding center also must be reexamined in light of repeated findings that aphagia and starvation can be obtained with lesions or knife cuts that spare the lateral hypothalamus (e.g., Albert, Storlien, Wood, & Ehman, 1970; Gold, 1967; Grossman & Grossman, 1971; Morgane, 1961a). These findings are consistent with the fact that the most effective placements for the production of feeding deficits have been localized in the far-lateral aspects of the tuberal hypothalamus (Anand & Brobeck, 1951; Morgane, 1961b; Oltmans & Harvey, 1972), a region consisting largely of ascending and descending fibers of passage rather than compact cellular masses (Morgane, 1969). Destruction of one particular pathway, the dopamine-containing neurons of the nigrostriatal bundle, has been emphasized by Ungerstedt (1971), since that pathway is damaged by effective LH lesions as well as by extrahypothalamic lesions that result in similar behavioral impairments (see also Fibiger, Zis, & McGeer, 1973; Marshall, Richardson, & Teitelbaum, 1974; Zigmond & Stricker, 1972).

The seminal experiments by Teitelbaum and his colleagues, which showed that voluntary feeding behavior would ultimately reappear if rats with LH lesions were initially maintained by intragastric intubations of liquid nutrients (Teitelbaum & Epstein, 1962; Teitelbaum & Stellar, 1954), have been replicated using rats with extrahypothalamic, dopamine-depleting lesions (e.g., Marshall et al., 1974; Zigmond & Stricker, 1973). A recent neurochemical model of the "lateral hypothalamic syndrome," proposed by Stricker and Zigmond (1976), suggests that destruction of central dopaminergic fibers disrupts not the differentiating aspects of specific motivated behaviors but a nonspecific activational component that is common to all motivation. This hypothesis accounts for the broad range of motivated activities that are disrupted by LH or other dopamine-depleting brain lesions, such as feeding, drinking, maternal, and thermoregulatory behaviors (e.g., Avar & Monos, 1969; Satinoff & Shan, 1971; Stricker, 1976; Stricker & Zigmond, 1974) as well as for the reversal of these deficits by such nonspecific activators as amphetamine, caffeine, tail pinch, and environmental stress (Antelman & Rowland, 1975; Marshall, Levitan, & Stricker, 1976; Stricker & Zigmond, 1976; Teitelbaum & Wolgin, 1975). Noncatecholaminergic pathways, as yet unidentified, presumably mediate the specific signals for hunger and other drives (Stricker & Zigmond, 1976).

The broad disruption of behavior following LH lesions apparently accounts for the alterations in food intake and body weight that are observed following combined VMH and LH lesions. The effects of combined lesions do not cancel one another as might be predicted by the set point hypothesis of Keesey and Powley (1975). Instead, rats become aphagic and lose weight initially (Anand & Brobeck, 1951), but later, after they resume feeding behavior, they become hyperphagic and obese (Williams & Teitelbaum, 1959). While the ventromedial and lateral hypothalamus thus do not simply determine a body weight set point, or serve as satiety and feeding centers, they may nevertheless contribute to the control of peripheral metabolism (Frohman, 1971). Indeed, following consumption of a meal, electrophysiological activity in the ventromedial hypothalamus is known to increase, while that in the lateral hypothalamus decreases or does not change (Anand, Chhina, Sharma, Dua, & Singh, 1964; Anand

& Pillai, 1967; Oomura et al., 1964). Furthermore, electrical stimulation of loci in the hypothalamus has been shown to alter carbohydrate metabolism in the liver, with sympathetic nerves being activated by stimulation in medial areas and parasympathetic fibers activated by more lateral placements (Shimazu, Fukuda, & Ban, 1966). It therefore seems possible that LH lesions alter fat metabolism toward increased lipolysis, mirroring the effects of VMH lesions (see also Steffens, Mogenson, & Stevenson, 1972). This hypothesis, which resembles a central feature of the recent proposal by Keesey and Powley (1975) without subscribing to their notions about body weight set point, awaits experimental investigation.

Origin of the Stimulus for Hunger

Receptors that monitor changes in the availability of utilizable nutrients may be located in the brain. Indeed, central receptors are well known to trigger a massive sympathetic discharge when stimulated during insulin-induced hypoglycemia (Cannon, McIver, & Bliss, 1924). Such receptors are presumably involved in mediating the hyperglycemia and associated feeding responses that are seen in rats after intracranial injections of 2-DG (Miselis & Epstein, 1975; Müller, Cocchi, & Forni, 1971), although, as noted earlier, the specific stimulus that activates them may not be a decrease in the utilization of glucose per se (Fiorentini & Müller, 1975; Flatt et al., 1974; Hetenyi, 1972; Friedman et al., Note 1). However, it is not likely that pronounced decreases in cerebral glycolysis ever occur except under nonphysiological experimental conditions, because the brain is normally protected from such emergencies. Thus, the usual stimulus for hunger should be sought elsewhere.

Our recent findings that insulin-induced feeding is abolished by infusions of fructose, but not ketone bodies, strongly implicate the liver as the origin of the hunger signal (Friedman et al., Note 1). The liver appears to be a likely site for peripheral receptors because of its strategic location and critical involvement in the traffic of metabolic fuels from both exogenous and endogenous sources. In the postabsorptive state, when hunger normally occurs, glucogenic precursors are diverted from energy production to the service of gluconeogenesis. The liver then becomes increasingly dependent on the supply of free fatty acids from adipose tissue, but free fatty acids are converted to ketone bodies in proportion to their availability (Van Harken, Dixon, & Heimberg, 1969). Although total hepatic energy production may not be compromised (Mayes & Felts, 1967), it is tempting to speculate that the shift in substrate flow away from the tricarboxylic acid cycle somehow provides the signal for hunger.

A decrease in oxidative metabolism in the liver would be expected when there is a decline in the supply of utilizable fuels to that organ, as following large doses of insulin or 2-DG, and that change may contribute to the observed feeding response. Alterations in oxidative metabolism also may account for the appearance of hunger in the postabsorptive state, when the flood of nutrients to the liver abates and fuels are diverted from tricarboxylic-acid-cycle activity toward gluconeogenesis and ketogenesis. In this regard, note that hepatic glucose production in rats is increased both after VMH lesions (Holm et al., 1973) and during alloxan diabetes (Friedmann, Goodman, & Weinhouse, 1967), the two conditions in which chronic hyperphagia is most prominent. Glucose output also is increased after 2 hours of fasting (Schimmel & Knobil, 1970), at which time feeding may be expected (Snowdon, 1970). On the other hand, note that hunger is not associated with enhanced glucose output when the supply of utilizable fuels for the liver is abundant, as occurs when rats are fed high-protein or high-fat diets (Eisenstein, Strack, & Steiner, 1974).

An important role for the liver in stimulating hunger has been advocated previously, most notably by Russek (1963, 1971). In support of his position, Russek (1970) has demonstrated that infusions of glucose directly into the portal vein can depress food intake in hungry animals (see also Booth & Jarman, in press; Campbell & Davis, 1974; Novin, Sanderson, & VanderWeele, 1974). In addition, feeding by fasted animals results in a prompt reversal of hepatic metabolism toward glycogen formation (Foster, 1967;

Mayes, 1962).[3] While these results clearly are consistent with Russek's (1975) notion of a hepatic glucoreceptor participating in the "glycogenostatic" control of hunger, they neither specify the critical event nor do they demand that it is a change in the metabolism of glucose per se. Indeed, intragastric injections of fatty acids and intermediary metabolites similarly reduce feeding in mildly hungry animals, after a delay suitable for absorption, in proportion to the estimated energy yield of the load (Booth, 1972c, 1972d; Booth & Jarman, in press). Moreover, a model based on changes in liver glycogen levels or glycolysis rates cannot explain recent findings that despite pronounced depletions of liver glycogen, overeating did not occur in diabetic rats fed a high-fat diet (Friedman, 1975). Collectively, these observations are instead consistent with our suggestion that alterations in hepatic oxidative metabolism provide the stimuli for hunger and satiety.

In order for hepatic events to have behavioral repercussions they must influence the brain. Both blood-borne and neural signals should be considered, but unfortunately, there are few unambiguous data at present that bear on this point. Nevertheless, it is interesting to note that electrical stimulation of the vagus has been found to elicit feeding in satiated cats (Peñaloza-Rojas, Barrera-Mera, & Kubli-Garfias, 1969), while DC blockade of the vagus decreases feeding in hungry cats (Peñaloza-Rojas & Russek, 1963). Furthermore, portal infusions of glucose have been shown to affect the firing rates of afferent fibers from the liver (Niijima, 1969) as well as single neurons in the hypothalamus (Schmitt, 1973). Taken together with the apparent centrifugal influence on liver function (Ban, 1967; Frohman, 1971), these observations raise the admittedly speculative but exciting possibility of an interaction between the brain and the liver in the control of food intake and energy metabolism.

[3] According to our proposal, this shift in metabolism would tend to remove hunger as a stimulus for feeding rather early in the meal, and the increasing dependence of ingestion on nonmetabolic factors (e.g., palatability of the diet) might explain why meal sizes are so unpredictable (Le Magnen & Tallon, 1966). Because metabolic shifts within the liver are strongly influenced by fluctuations in insulin level, or in insulin/glucagon ratios (Cahill et al., 1966; Exton & Park, 1967; Friedman et al., 1967; Menahan & Wieland, 1969; Seyffert & Madison, 1967), such endocrine changes might have a considerable indirect effect on satiety (cf. de Castro & Balagura, 1975; Steffens, 1975).

Summary and Conclusions

Many physiological changes occur with the development of hunger. As we have seen, insulin secretion diminishes as the gastrointestinal tract empties, and the utilization of glucose in cells that are dependent on insulin for its entry decreases too. Conversely, there is an increase in the secretions of glucagon, growth hormone, and epinephrine, all of which provide for the mobilization of glucose and lipid from body stores. Almost every one of these correlated events has provided a basis for a single-factor theory concerning the physiological stimulus for hunger (e.g., Kennedy, 1953; Mayer, 1953; Snowdon, 1970; Woods, Decke, & Vasselli, 1974). However, we believe these theories have focused on secondary issues and have missed the phenomenon at the core—namely, the continued availability of diverse metabolic fuels to maintain the energy supply (Adolph, 1947; Booth, 1972c, 1972d; Ugolev & Kassil, 1961).

Hunger usually is associated with a decreased supply of fuels from the intestines. Elaborate physiological and biochemical mechanisms can maintain energy production in the postabsorptive state, and the internal reserves they draw on are adaptively doled out in response to tissue needs. The principle storage reserve is fat. When the lipid supply from adipose tissue is unusually abundant, this surplus is utilized and hunger is forestalled. However, when the availability of fat is relatively low, the need for exogenous fuels increases. The liver is the organ that is most responsive to differences of this kind in the supply of metabolic fuels from both endogenous and exogenous sources. We propose that the stimulus for hunger arises in the liver, when fuel delivery from the intestines and adipose tissue is inadequate for the maintenance of bodily functions without significant hepatic contributions. The stimulus for hunger may be associated with some shift in hepatic metabolism, and food intake may

reverse that change. In other words, it is the liver that may integrate information about caloric homeostasis and provide the specific stimulus for hunger to the brain, and it is the liver whose function seems to be most affected by feeding and thus allow rapid feedback for the termination of hunger.

This discussion has been directed solely toward deducing the metabolic factors that might underlie the urge to eat. However, we recognize that animals with nutritional needs may not choose to eat, and that animals with no such needs may eat anyway. Although we have neglected these issues, we do not wish to minimize their importance or the significance of additional questions regarding the recognition, detection, and selection of food, the effects on feeding of individual experience, learning, affective state, competing drives, and the like. Indeed, these psychological variables ultimately will have to be integrated with the physiological factors to obtain a balanced appreciation of feeding behavior. From this broad context we have selected hunger as a single issue for consideration and have emphasized the following two points.

First, we do not find it useful to divide the signals for hunger into glucostatic and lipostatic, subserving short-term and long-term controls of food intake. Instead, we believe that hunger appears and disappears according to normally occurring fluctuations in the availability of utilizable metabolic fuels, regardless of which fuels they are and how full the storage reserves.

Second, we believe that the traditional description of central control mechanisms in terms of feeding and satiety *centers* or *systems* cannot be maintained in light of recent evidence. Instead, lateral hypothalamic lesions appear to interrupt all motivated behaviors, not just feeding, while ventromedial hypothalamic lesions primarily disrupt nutrient processing so that animals cannot readily obtain fuel from bodily stores.

These conclusions have been reached by taking a physiological approach in considering the physiological basis of hunger. This may seem ironic, but physiological psychology has traditionally contained little classical physiology and instead has found its evolutionary roots in neurology. Thus, while the Sherringtonian metaphor of reciprocal excitatory and inhibitory controls is evident in the popular theories of dual hypothalamic centers and body weight set points, we believe that hunger and satiety are more appropriately analogous to the coordinated mechanisms that normally control gluconeogenesis and lipogenesis (cf. Tepperman & Tepperman, 1970). We hope that future work on the physiological basis of hunger will focus on these pathways of metabolism instead of so exclusively pursuing pathways in the brain.

REFERENCE NOTE

1. Friedman, M. I., Rowland, N., Saller, C. F., & Stricker, E. M. *Homeostasis during hypoglycemia: Central control of adrenal secretion and peripheral control of feeding.* Manuscript submitted for publication, 1976.

REFERENCES

Adolph, E. F. Urges to eat and drink in rats. *American Journal of Physiology,* 1947, *151,* 110–125.

Ahlskog, J. E., & Hoebel, B. G. Overeating and obesity from damage to a noradrenergic system in the brain. *Science,* 1973, *182,* 166–169.

Ahlskog, J. E., Hoebel, B. G., & Breisch, S. T. Hyperphagia following lesions of the noradrenergic pathway is prevented by hypophysectomy. *Federation Proceedings,* 1974, *33,* 463. (Abstract)

Ahlskog, J. E., Randall, P. K., & Hoebel, B. G. Hypothalamic hyperphagia: Dissociation from hyperphagia following destruction of noradrenergic neurons. *Science,* 1975, *190,* 399–401.

Albert, D. J., & Storlien, L. H. Hyperphagia in rats with cuts between the ventromedial and lateral hypothalamus. *Science,* 1969, *165,* 599–600.

Albert, D. J., Storlien, L. H., Wood, D. J., & Ehman, G. K. Further evidence for a complex system controlling feeding behavior. *Physiology and Behavior,* 1970, *5,* 1075–1082.

Alonso, L. G., & Maren, T. H. Effect of food restriction on body composition of hereditary obese mice. *American Journal of Physiology,* 1955, *183,* 284–290.

Anand, B. K. Nervous regulation of food intake. *Physiological Reviews,* 1961, *41,* 677–708.

Anand, B. K., & Brobeck, J. R. Hypothalamic control of food intake in rats and cats. *Yale Journal of Biology and Medicine,* 1951, *24,* 123–140.

Anand, B. K., Chhina, G. S., Sharma, K. N., Dua, S., & Singh, B. Activity of single neurons in the hypothalamic feeding centers: Effect of glucose. *American Journal of Physiology,* 1964, *207,* 1146–1154.

Anand, B. K., & Pillai, R. V. Activity of single neurons in the hypothalamic feeding centres: Effect of gastric distension. *Journal of Physiology,* 1967, *192,* 63–67.

Antelman, S. M., & Rowland, N. Hyperphagia in normal rats and recovery of behavioral deficits in

rats with lateral hypothalamic lesions: Stress-induced effects related to the nigrostriatal dopamine system. *Psychosomatic Medicine,* 1975, *37,* 81. (Abstract)

Arees, A. E., Veltman, B. I., & Mayer, J. Hypothalamic blood flow following goldthioglucose-induced lesions. *Experimental Neurology,* 1969, *25,* 410–415.

Avar, Z., & Monos, E. Biological role of lateral hypothalamic structures participating in the control of maternal behaviour in the rat. *Acta Physiologica* (Academy of Science, Hungary), 1969, *35,* 285–294.

Balagura, S., & Devenport, L. D. Feeding patterns of normal and ventromedial hypothalamic lesioned male and female rats. *Journal of Comparative and Physiological Psychology,* 1970, *71,* 357–364.

Ban, T. The hypothalamus and liver metabolism. *Acta Neurovegetativa,* 1967, *30,* 137–144.

Bates, M. W., Mayer, J., & Nauss, S. F. Fat metabolism in three forms of experimental obesity: Acetate incorporation. *American Journal of Physiology,* 1955, *180,* 304–308.

Björntorp, P., Bergman, H., & Varnauskas, E. Plasma free fatty acid turnover rate in obesity. *Acta Medica Scandinavica,* 1969, *185,* 351–356.

Booth, D. A. Conditioned satiety in the rat. *Journal of Comparative and Physiological Psychology,* 1972, *81,* 457–471. (a)

Booth, D. A. Feeding inhibition by glucose loads, compared between normal and diabetic rats. *Physiology and Behavior,* 1972, *8,* 801–805. (b)

Booth, D. A. Postabsorptively induced suppression of appetite and the energostatic control of feeding. *Physiology and Behavior,* 1972, *9,* 199–202. (c)

Booth, D. A. Satiety and behavioral caloric compensation following intragastric glucose loads in the rat. *Journal of Comparative and Physiological Psychology,* 1972, *78,* 412–432. (d)

Booth, D. A. Some characteristics of feeding during streptozotocin-induced diabetes in the rat. *Journal of Comparative and Physiological Psychology,* 1972, *80,* 238–249. (e)

Booth, D. A., & Jarman, S. P. Inhibition of food intake in the rat following complete absorption of glucose delivered into the stomach, intestine or liver. *Journal of Physiology,* in press.

Booth, D. A., & Toates, F. M. A physiological control theory of food intake in the rat: Mark I. *Bulletin of the Psychonomic Society,* 1974, *3,* 442–444.

Booth, D. A., Toates, F. M., & Platt, S. V. Control system for hunger and its implications in animal and man. In D. Novin, W. Wyrwicka, & G. Bray (Eds.), *Hunger: Basic mechanisms and clinical implications.* New York: Raven Press, 1976.

Breisch, S. T., Zemlan, F. P., & Hoebel, B. G. Hyperphagia and obesity following serotonin depletion by intraventricular parachlorophenylalanine. *Science,* 1976, *192,* 383–385.

Brobeck, J. R. Mechanisms of the development of obesity in animals with hypothalamic lesions. *Physiological Reviews,* 1946, *26,* 541–559.

Brobeck, J. R. Food intake as a mechanism of temperature regulation. *Yale Journal of Biology and Medicine,* 1948, *20,* 545–552.

Brobeck, J. R. Neural regulation of food intake. *Annals of the New York Academy of Sciences,* 1955, *63,* 44–55.

Brobeck, J. R. Nature of satiety signals. *American Journal of Clinical Nutrition,* 1975, *28,* 806–807.

Brobeck, J. R., Tepperman, J., & Long, C. N. H. Experimental hypothalamic hyperphagia in the albino rat. *Yale Journal of Biology and Medicine,* 1943, *15,* 831–853.

Brodows, R. G., Pi-Sunyer, F. X., & Campbell, R. G. Sympathetic control of hepatic glycogenolysis during glucopenia in man. *Metabolism,* 1975, *24,* 617–624.

Brooks, C. McC., Lockwood, R. A., & Wiggins, M. L. A study of the effect of hypothalamic lesions on the eating habits of the albino rat. *American Journal of Physiology,* 1946, *147,* 735–741.

Caffyn, Z. E. Y. Early vascular changes in the brain of the mouse after injections of goldthioglucose and bipiperidyl mustard. *Journal of Pathology,* 1972, *106,* 49–56.

Cahill, G. F., Jr. Starvation in man. *New England Journal of Medicine,* 1970, *282,* 668–675.

Cahill, G. F., Jr. et al. Hormone-fuel interrelationships during fasting. *Journal of Clinical Investigation,* 1966, *45,* 1751–1769.

Campbell, C. S., & Davis, J. D. Licking rate of rats is reduced by intraduodenal and intraportal glucose infusion. *Physiology and Behavior,* 1974, *12,* 357–365.

Cannon, W. B., McIver, M. A., & Bliss, S. W. Studies on the conditions of activity in endocrine glands. XIII. A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia. *American Journal of Physiology,* 1924, *69,* 46–60.

Carlson, A. J. *The control of hunger in health and disease.* Chicago: University of Chicago Press, 1916.

Castro, J. M. de, & Balagura, S. Meal patterning in the streptozotocin-diabetic rat. *Physiology and Behavior,* 1975, *15,* 259–263.

Cohn, C., & Joseph, D. Influence of body weight and body fat on appetite of "normal" lean and obese rats. *Yale Journal of Biology and Medicine,* 1962, *34,* 598–607.

Connor, R. E., & Newberne, P. M. Forced weight reduction and lipogenesis in rat adipocytes. *Nutrition Reports International,* 1974, *10,* 305–314.

Crone, C. Facilitated transfer of glucose from blood into brain tissue. *Journal of Physiology,* 1965, *181,* 103–113.

Daniel, P. M., Love, E. R., & Pratt, O. E. Insulin and the way the brain handles glucose. *Journal of Neurochemistry,* 1975, *25,* 471–476.

Davis, J. D., Campbell, C. S., Gallagher, R. J., & Zurakov, M. A. Disappearance of a humoral satiety factor during food deprivation. *Journal of Comparative and Physiological Psychology,* 1971, *75,* 476–482.

Debons, A. F., Krimsky, I., & From, A. A direct action of insulin on the hypothalamic satiety center. *American Journal of Physiology,* 1970, *219*, 938–943.

Debons, A. F., Krimsky, I., Likuski, H. J., From, A., & Cloutier, R. J. Goldthioglucose damage to the satiety center: Inhibition in diabetes. *American Journal of Physiology,* 1968, *214*, 652–658.

DiGirolamo, M., & Rudman, D. Variations in glucose metabolism and sensitivity to insulin of the rat's adipose tissue in relation to age and body weight. *Endocrinology,* 1968, *82*, 1133–1141.

Drenick, E. J., Alvarez, L. C., Tamasi, G. C., & Brickman, A. S. Resistance to symptomatic insulin reactions after fasting. *Journal of Clinical Investigation,* 1972, *51*, 2757–2762.

Eisenstein, A. B., Strack, I., & Steiner, A. Increased hepatic glucogenesis without a rise of glucagon secretion in rats fed a high fat diet. *Diabetes,* 1974, *23*, 869–875.

Epstein, A. Reciprocal changes in feeding behavior produced by intrahypothalamic chemical injections. *American Journal of Physiology,* 1960, *199*, 969–974.

Epstein, A. N., Nicolaidis, S., & Miselis, R. The glucoprivic control of food intake and the glucostatic theory of feeding behavior. In G. J. Mogenson & F. R. Calaresu (Eds.), *Neural integration of physiological mechanisms and behaviour.* Toronto: University of Toronto Press, 1975.

Epstein, A. N., & Teitelbaum, P. Specific loss of the hypoglycemic control of feeding in recovered lateral rats. *American Journal of Physiology,* 1967, *213*, 1159–1167.

Exton, J. H. Gluconeogenesis. *Metabolism,* 1972, *21*, 945–990.

Exton, J. H., & Park, C. R. The role of cyclic AMP in the control of liver metabolism. In G. Weber (Ed.), *Advances in enzyme regulation.* Oxford: Pergamon Press, 1967.

Farner, D. S., Oksche, A., Kamemoto, F. I., King, J. R., & Cheyney, H. E. A comparison of the effect of long daily photoperiods on the pattern of energy storage in migratory and non-migratory finches. *Comparative Biochemistry and Physiology,* 1961, *2*, 125–142.

Felig, P. The glucose-alanine cycle. *Metabolism,* 1973, *22*, 179–207.

Felig, P., Owen, O. E., Wahren, J., & Cahill, G. F., Jr. Amino acid metabolism during prolonged starvation. *Journal of Clinical Investigation,* 1969, *48*, 584–594.

Fibiger, H. C., Zis, A. P., & McGeer, E. G. Feeding and drinking deficits after 6-hydroxydopamine administration in the rat: Similarities to the lateral hypothalamic syndrome. *Brain Research,* 1973, *55*, 135–148.

Fiorentini, A., & Müller, E. E. Sensitivity of central chemoreceptors controlling blood glucose and body temperature during glucose deprivation. *Journal of Physiology,* 1975, *248*, 247–271.

Flatt, J. P., & Blackburn, G. L. The metabolic fuel regulatory system: Implications for protein-sparing therapies during caloric deprivation and disease. *American Journal of Clinical Nutrition,* 1974, *27*, 175–187.

Flatt, J. P., Blackburn, L., Randers, G., & Stanbury, J. B. Effects of ketone body infusion on hypoglycemic reaction in postabsorptive dogs. *Metabolism,* 1974, *23*, 151–158.

Foster, D. W. Studies in the ketosis of fasting. *Journal of Clinical Investigation,* 1967, *46*, 1283–1296.

Friedman, M. I. Effects of alloxan diabetes on hypothalamic hyperphagia and obesity. *American Journal of Physiology,* 1972, *222*, 174–178.

Friedman, M. I. Evidence that control of food intake is based on immediate availability of utilizable fuels. *Federation Proceedings,* 1975, *34*, 374. (Abstract)

Friedmann, B., Goodman, E. H., Jr., & Weinhouse, S. Effects of insulin and fatty acids on gluconeogenesis in the rat. *Journal of Biological Chemistry,* 1967, *242*, 3620–3627.

Frohman, L. A. The hypothalamus and metabolic control. In H. L. Ioachim (Ed.), *Pathobiology annual* (Vol. 1). New York: Appleton-Century-Crofts, 1971.

Frohman, L. A., & Bernardis, L. L. Growth hormone and insulin levels in weanling rats with ventromedial hypothalamic lesions. *Endocrinology,* 1968, *82*, 1125–1132.

Frohman, L. A., Goldman, J. K., & Bernardis, L. L. Metabolism of intravenously injected ^{14}C-glucose in weanling rats with hypothalamic obesity. *Metabolism,* 1972, *21*, 799–805.

Frohman, L. A., Müller, E. E., & Cocchi, D. Central nervous system mediated inhibition of insulin secretion due to 2-deoxy-glucose. *Hormone and Metabolic Research,* 1973, *5*, 21–26.

Gold, R. M. Aphagia and adipsia following unilateral and bilaterally asymmetrical lesions in rats. *Physiology and Behavior,* 1967, *2*, 211–220.

Gold, R. M. Hypothalamic hyperphagia produced by parasagittal knife cuts. *Physiology and Behavior,* 1970, *5*, 23–25.

Goldman, J. K., & Bernardis, L. L. Gluconeogenesis in weanling rats with hypothalamic obesity. *Hormone and Metabolic Research,* 1975, *7*, 148–152.

Goldman, J. K., Schnatz, J. D., Bernardis, L. L., & Frohman, L. A. Adipose tissue metabolism of weanling rats after destruction of ventromedial hypothalamic nuclei: Effect of hypophysectomy and growth hormone. *Metabolism,* 1970, *19*, 995–1005.

Goldman, J. K., Schnatz, J. D., Bernardis, L. L., & Frohman, L. A. Effects of ventromedial hypothalamic destruction in rats with preexisting streptozotocin-induced diabetes. *Metabolism,* 1972, *21*, 132–136. (a)

Goldman, J. K., Schnatz, J. D., Bernardis, L. L., & Frohman, L. A. *In vivo* and *in vitro* metabolism in hypothalamic obesity. *Diabetologia,* 1972, *8*, 160–164. (b)

Goldrick, R. B., & McLoughlin, G. M. Lipolysis and lipogenesis from glucose in human fat cells of different sizes: Effects of insulin, epinephrine, and

theophylline. *Journal of Clinical Investigation,* 1970, *49*, 1213–1223.

Grossman, S. P. The VMH: A center for affective reactions, satiety, or both? *Physiology and Behavior,* 1966, *1*, 1–10.

Grossman, S. P., & Grossman, L. Food and water intake in rats with parasagittal knife cuts medial or lateral to the lateral hypothalamus. *Journal of Comparative and Physiological Psychology,* 1971, *74*, 148–156.

Haessler, H. A., & Crawford, J. D. Alterations in the fatty acid composition of depot fat associated with obesity. *Annals of the New York Academy of Sciences,* 1965, *131*, 476–484.

Haessler, H. A., & Crawford, J. D. Fatty acid composition and metabolic activity of depot fat in experimental obesity. *American Journal of Physiology,* 1967, *213*, 255–261.

Han, P. W. Hypothalamic obesity in rats without hyperphagia. *Transactions of the New York Academy of Sciences,* 1967, *30*, 229–243.

Han, P. W., & Frohman, L. A. Hyperinsulinemia in tube-fed hypophysectomized rats bearing hypothalamic lesions. *American Journal of Physiology,* 1970, *219*, 1632–1636.

Hartman, A. D., Cohen, A. I., Richane, C. J., & Hsu, T. Lipolytic response and adenyl cyclase activity of rat adipocytes as related to cell size. *Journal of Lipid Research,* 1971, *12*, 498–505.

Havel, R. J. Caloric homeostasis and disorders of fuel transport. *New England Journal of Medicine,* 1972, *287*, 1186–1192.

Havel, R. J., & Goldfien, A. The role of the sympathetic nervous system in the metabolism of free fatty acids. *Journal of Lipid Research,* 1959, *1*, 102–108.

Hernandez, L., MacKenzie, R., & Hoebel, B. G. Differential dose-related effects of portal and jugular 2-deoxy-D-glucose (2DG) injections on feeding in rats. *Federation Proceedings,* 1976, *35*, 760. (Abstract)

Hervey, G. R. The effects of lesions in the hypothalamus in parabiotic rats. *Journal of Physiology,* 1959, *145*, 336–352.

Hetenyi, G., Jr. Effect of mannose, fructose and hydroxybutyrate on the hepatic response to hypoglycemia. *Diabetes,* 1972, *21*, 797–804.

Hetherington, A. W., & Ranson, S. W. Hypothalamic lesions and adiposity in the rat. *Anatomical Record,* 1940, *78*, 149–172.

Hoebel, B. G., & Teitelbaum, P. Weight regulation in normal and hypothalamic hyperphagic rats. *Journal of Comparative and Physiological Psychology,* 1966, *61*, 189–193.

Hökfelt, B., & Bydgeman, S. Increased adrenaline production following administration of 2-deoxy-D-glucose in the rat. *Proceedings of the Society for Experimental Biology and Medicine,* 1961, *106*, 537–539.

Holm, H., Hustvedt, B.-E., & Løvø, A. Protein metabolism in rats with ventromedial hypothalamic lesions. *Metabolism,* 1973, *22*, 1377–1387.

Horton, R. W., Meldrum, B. S., & Bachelard, H. S. Enzymic and cerebral metabolic effects of 2-deoxy-D-glucose. *Journal of Neurochemistry,* 1973, *21*, 507–520.

Hustvedt, B.-E., & Løvø, A. Correlation between hyperinsulinemia and hyperphagia in rats with ventromedial hypothalamic lesions. *Acta Physiologica Scandinavica,* 1972, *84*, 29–33.

Hustvedt, B.-E., & Løvø, A. Rapid effect of ventromedial hypothalamic lesions on lipogenesis in rats. *Acta Physiologica Sandinavica,* 1973, *87*, 28A–29A.

Issekutz, B., Jr., Bortz, W. M., Miller, H. I., & Paul, P. Turnover rate of plasma FFA in humans and in dogs. *Metabolism,* 1967, *16*, 1001–1009.

Janes, R. G., & Prosser, M. Influence of high fat diets on alloxan diabetes. *American Journal of Physiology,* 1947, *151*, 581–587.

Janowitz, H. D., & Ivy, A. C. Role of blood sugar levels in spontaneous and insulin-induced hunger in man. *Journal of Applied Physiology,* 1949, *1*, 643–645.

Jeanrenaud, B. Adipose tissue dynamics and regulation, revisited. *Ergebnisse der Physiologie,* 1968, *60*, 57–140.

Johnson, P. R., Stern, J. S., Greenwood, M. R. C., Zucker, L. M., & Hirsch, J. Effect of early nutrition on adipose cellularity and pancreatic insulin release in the Zucker rat. *Journal of Nutrition,* 1973, *103*, 738–743.

Keesey, R. E., & Powley, T. L. Hypothalamic regulation of body weight. *American Scientist,* 1975, *63*, 558–565.

Kendeigh, S. C., Kontogiannis, J. E., Mazac, A., & Roth, R. R. Environmental regulation of food intake by birds. *Comparative Biochemistry and Physiology,* 1969, *31*, 941–957.

Kennedy, G. C. The hypothalamic control of food intake in rats. *Proceedings of the Royal Society, London,* 1950, *Series B, 137*, 535–549.

Kennedy, G. C. The role of depot fat in the hypothalamic control of food intake in the rat. *Proceedings of the Royal Society, London,* 1953, *Series B, 140*, 578–592.

Kennedy, G. C. The central nervous regulation of calorie balance. *Proceedings of the Nutrition Society,* 1961, *20*, 58–64.

Klain, G. J., & Rogers, G. B. Seasonal changes in adipose tissue lipogenesis in the hibernator. *International Journal of Biochemistry,* 1970, *1*, 248–250.

Knittle, J. L., & Hirsch, J. Effect of early nutrition on the development of rat epididymal fat pads: Cellularity and metabolism. *Journal of Clinical Investigation,* 1968, *47*, 2091–2098.

Krebs, H. A., & Hems, R. Fatty acid metabolism in the perfused rat liver. *Biochemical Journal,* 1970, *119*, 525–533.

Krebs, H. A., Williamson, D. H., Bates, M. W., Page, M. A., & Hawkins, R. A. The role of ketone bodies in caloric homeostasis. *Advances in Enzyme Regulation,* 1971, *9*, 387–409.

Le Magnen, J. Advances in studies on the physiological control and regulation of food intake. In E. Stellar & J. M. Sprague (Eds.), *Progress in*

physiological psychology (Vol. 4). New York: Academic Press, 1971.

Le Magnen, J., & Devos, M. Metabolic correlates of the meal onset in the free food intake of rats. *Physiology and Behavior,* 1970, *5,* 805–814.

Le Magnen, J., Devos, M., Gaudilliere, J.-P., Louis-Sylvestre, J., & Tallon, S. Role of a lipostatic mechanism in regulation by feeding of energy balance in rats. *Journal of Comparative and Physiological Psychology,* 1973, *84,* 1–23.

Le Magnen, J., & Tallon, S. La périodicité spontanée de la prise d'aliments *ad libitum* du rat blanc. *Journal de Physiologie* (Paris), 1966, *58,* 323–349.

Levine R., & Haft, D. E. Carbohydrate homeostasis. *New England Journal of Medicine,* 1970, *283,* 175–183; 237–246.

Lewinska, M. K., & Romaniuk, A. Is the ventromedial nucleus of the hypothalamus a "satiation center"? *Acta Biologiae Experimentalis* (Warsaw), 1966, *26,* 285–297.

Louis-Sylvestre, J. Preabsorptive insulin release and hypoglycemia in rats. *American Journal of Physiology,* 1976, *230,* 56–60.

Løvø, A., & Hustvedt, B.-E. Correlation between altered acetate utilization and hyperphagia in rats with ventromedial hypothalamic lesions. *Metabolism,* 1973, *22,* 1459–1465.

Lyon, J. B., Jr., Dowling, M. T., & Fenton, P. F. Studies in obesity: II. Food intake and oxygen consumption. *Journal of Nutrition,* 1953, *51,* 65–70.

MacKay, E. M., Callaway, J. W., & Barnes, R. H. Hyperalimentation in normal animals produced by protamine insulin. *Journal of Nutrition,* 1940, *20,* 59–66.

Maddock, S., Hawkins, J. E., Jr., & Holmes, E. The inadequacy of substances of the "glucose cycle" for maintenance of normal cortical potentials during hypoglycemia produced by hepatectomy with abdominal evisceration. *American Journal of Physiology,* 1939, *125,* 551–565.

Marliss, E. B., Aoki, T. T., Unger, R. H., Soeldner, J. S., & Cahill, G. F., Jr. Glucagon levels and metabolic effects in fasting man. *Journal of Clinical Investigation,* 1970, *49,* 2256–2270.

Marshall, J. F. Increased orientation to sensory stimuli following medial hypothalamic damage in rats. *Brain Research,* 1975, *86,* 373–387.

Marshall, J. F., Levitan, D., & Stricker, E. M. Activation-induced restoration of sensorimotor functions in rats with dopamine-depleting brain lesions. *Journal of Comparative and Physiological Psychology,* 1976, *90,* 536–546.

Marshall, J. F., Richardson, J. S., & Teitelbaum, P. Nigrostriatal bundle damage and the lateral hypothalamic syndrome. *Journal of Comparative and Physiological Psychology,* 1974, *87,* 808–830.

Marshall, J. F., & Teitelbaum, P. A comparison of the eating in response to hypothermic and glucoprivic challenges after nigral 6-hydroxydopamine and lateral hypothalamic electrolytic lesions in rats. *Brain Research,* 1973, *55,* 229–233.

Martin, R. J., & Lamprey, P. Changes in liver and adipose tissue enzymes and lipogenesis activities during the onset of hypothalamic obesity in mice. *Life Sciences,* 1974, *14,* 1121–1131.

Mayer, J. The glucostatic theory of regulation of food intake and the problem of obesity. *Bulletin of the New England Medical Center,* 1952, *14,* 43–49.

Mayer, J. Glucostatic mechanisms of regulation of food intake. *New England Journal of Medicine,* 1953, *249,* 13–16.

Mayer, J. Regulation of energy intake and the body weight: The glucostatic theory and the lipostatic hypothesis. *Annals of the New York Academy of Sciences,* 1955, *63,* 15–42.

Mayer, J. Some advances in the study of the physiologic basis of obesity. *Metabolism,* 1957, *6,* 435–446.

Mayer, J., & Marshall, N. B. Specificity of gold thioglucose for ventromedial hypothalamic lesions and hyperphagia. *Nature,* 1956, *178,* 1399–1400.

Mayes, P. A. A calorie deficiency hypothesis of ketogenesis. *Metabolism,* 1962, *11,* 781–799.

Mayes, P. A., & Felts, J. M. Regulation of fat metabolism in the liver. *Nature,* 1967, *215,* 716–718.

McGinty, D., Epstein, A. N., & Teitelbaum, P. The contribution of oropharyngeal sensations to hypothalamic hyperphagia. *Animal Behaviour,* 1965, *13,* 413–418.

Meldrum, B. S., & Horton, R. W. Cerebral functional effects of 2-deoxy-D-glucose and 3-O-methylglucose in rhesus monkeys. *Electroencephalography and Clinical Neurophysiology,* 1973, *35,* 59–66.

Menahan, L. A., & Wieland, O. Interactions of glucagon and insulin on the metabolism of perfused livers from fasted rats. *European Journal of Biochemistry,* 1969, *9,* 55–62.

Miller, N. E., Bailey, C. J., & Stevenson, J. A. F. Decreased "hunger" but increased food intake resulting from hypothalamic lesions. *Science,* 1950, *112,* 256–259.

Miselis, R. R., & Epstein, A. N. Feeding induced by intracerebroventricular 2-deoxy-D-glucose in the rat. *American Journal of Physiology,* 1975, *229,* 1438–1447.

Morgane, P. J. Alterations in feeding and drinking behavior of rats with lesions in globi pallidi. *American Journal of Physiology,* 1961, *201,* 420–428. (a)

Morgane, P. J. Medial forebrain bundle and "feeding centers" of the hypothalamus. *Journal of Comparative Neurology,* 1961, *117,* 1–25. (b)

Morgane, P. J. The function of the limbic and the rhinic forebrain-limbic midbrain systems and reticular formation in the regulation of food and water intake. *Annals of the New York Academy of Sciences,* 1969, *157,* 806–848.

Mrosovsky, N. Hypothalamic hyperphagia without plateau in ground squirrels. *Physiology and Behavior,* 1974, *12,* 259–264.

Müller, E. E., Cocchi, D., & Forni, A. A central site for the hyperglycemic action of 2-deoxy-D-glucose

in mouse and rat. *Life Sciences,* 1971, *10,* 1057–1067.

Newsholme, E. A., & Start, C. *Regulation in metabolism.* London: Wiley, 1973.

Nicolaidis, S., Epstein, A. N., & Le Magnen, J. Effets de deux analogues du glucose (2-deoxy-D-glucose et 3-methyl-glucose) sur le metabolisme et le comportement alimentaire du rat. *Journal de Physiologie* (Paris), 1972, *65,* 150A.

Niijima, A. Afferent impulse discharges from glucoreceptors in the liver of the guinea pig. *Annals of the New York Academy of Sciences,* 1969, *157,* 690–700.

Novin, D., Sanderson, J. D., & VanderWeele, D. A. The effect of isotonic glucose on eating as a function of feeding condition and infusion site. *Physiology and Behavior,* 1974, *13,* 3–7.

Novin, D., VanderWeele, D., & Rezek, M. Infusion of 2-deoxy-D-glucose into the hepatic-portal system causes eating: Evidence for peripheral glucoreceptors. *Science,* 1973, *181,* 858–860.

Oltmans, G. A., & Harvey, J. A. LH syndrome and brain catecholamine levels after lesions of the nigrostriatal bundle. *Physiology and Behavior,* 1972, *8,* 69–78.

Oomura, Y. et al. Reciprocal activities of the ventromedial and lateral hypothalamic areas of cats. *Science,* 1964, *143,* 484–485.

Opsahl, C. A., & Powley, T. L. Failure of vagotomy to reverse obesity in the genetically obese Zucker rat. *American Journal of Physiology,* 1974, *226,* 34–38.

Owen, O. E. et al. Brain metabolism during fasting. *Journal of Clinical Investigation,* 1967, *46,* 1589–1595.

Owen, O. E., Felig, P., Morgan, A. P., Wahren, J., & Cahill, G. F., Jr. Liver and kidney metabolism during prolonged starvation. *Journal of Clinical Investigation,* 1969, *48,* 574–583.

Owen, O. E., & Reichard, G. A., Jr. Fuels consumed by man: The interplay between carbohydrates and fatty acids. *Progress in Biochemical Pharmacology,* 1971, *6,* 177–213. (a)

Owen, O. E., & Reichard, G. A., Jr. Human forearm metabolism during progressive starvation. *Journal of Clinical Investigation,* 1971, *50,* 1536–1545. (b)

Panksepp, J. Hypothalamic regulation of energy balance and feeding behavior. *Federation Proceedings,* 1974, *33,* 1150–1165.

Peñaloza-Rojas, J. H., Barrera-Mera, B., and Kubli-Garfias, C. Behavioral and brain electrical changes after vagal stimulation. *Experimental Neurology,* 1969, *23,* 378–383.

Peñaloza-Rojas, J. H., & Russek, M Anorexia produced by direct-current blockade of the vagus nerve. *Nature,* 1963, *200,* 126.

Pilcher, C. W. T., Jarman, S. P., & Booth, D. A. Route of glucose to the brain from food in the mouth of the rat. *Journal of Comparative and Physiological Psychology,* 1974, *87,* 56–61.

Powley, T. L., & Opsahl, C. A. Ventromedial hypothalamic obesity abolished by subdiaphragmatic vagotomy. *American Journal of Physiology,* 1974, *226,* 25–33.

Rabin, B. M. Effect of lesions of the ventro-medial hypothalamus on the electrical activity of the ventro-lateral hypothalamus. *Electroencephalography and Clinical Neurophysiology,* 1968, *25,* 344–350.

Rampone, A. J., & Shirasu, M. E. Temperature changes in the rat in response to feeding. *Science,* 1964, *144,* 317–319.

Randle, P. J. et al. Interactions of metabolism and the physiological role of insulin. *Recent Progress in Hormone Research,* 1966, *22,* 1–44.

Randle, P. J., Garland, P. B., Hales, C. N., & Newsholme, E. A. The glucose fatty-acid cycle: Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet,* 1963, *1,* 785–789.

Reynolds, R. W. Ventromedial hypothalamic lesions without hyperphagia. *American Journal of Physiology,* 1963, *204,* 60–62.

Richter, C. P. Increased dextrose appetite of normal rats treated with insulin. *American Journal of Physiology,* 1942, *135,* 781–787. (a)

Richter, C. P. Total self regulatory functions in animals and human beings. *Harvey Lectures,* 1942, *38,* 63–103. (b)

Richter, C. P., & Schmidt, E. C. H., Jr. Increased fat and decreased carbohydrate appetite of pancreatectomized rats. *Endocrinology,* 1941, *28,* 179–192.

Rowland, N., & Nicolaidis, S. Réponses glycémique et de prise d'aliments a l'injection intra-auriculaire et portale de 2-désoxy-*d*-glucose chez le rat. *Comptes Rendus des Seances de l'Academie des Sciences,* 1974, *279,* 1093–1096.

Rozin, P., & Mayer, J. Regulation of food intake in the goldfish. *American Journal of Physiology,* 1961, *201,* 968–974.

Russek, M. Participation of hepatic glucoreceptors in the control of intake of food. *Nature,* 1963, *197,* 79–80.

Russek, M. Demonstration of the influence of an hepatic glucosensitive mechanism on food-intake. *Physiology and Behavior,* 1970, *5,* 1207–1209.

Russek, M. Hepatic receptors and the neurophysiological mechanisms controlling feeding behavior. In S. Ehrenpreis & O. C. Solnitzky (Eds.), *Neurosciences research* (Vol. 4). New York: Academic Press, 1971.

Russek, M. Current hypotheses in the control of feeding behaviour. In G. J. Mogenson & F. R. Calaresu (Eds.), *Neural integration of physiological mechanisms and behaviour.* Toronto: University of Toronto Press, 1975.

Rutman, R. J., Lewis, F. S., & Bloomer, W. D. Bipiperidyl mustard, a new obesifying agent in the mouse. *Science,* 1966, *153,* 1000–1002.

Salans, L. B., Knittle, J. L., & Hirsch, J. The role of adipose cell size and adipose tissue insulin sensitivity in the carbohydrate intolerance of human obesity. *Journal of Clinical Investigation,* 1968, *47,* 153–165.

Saller, C. F., & Stricker, E. M. Hyperphagia and increased growth in rats after intraventricular injection of 5,7-dihydroxytryptamine. *Science,* 1976, *192*, 385–387.

Satinoff, E., & Shan, S. Y. Y. Loss of behavioral thermoregulation after lateral hypothalamic lesions in rats. *Journal of Comparative and Physiological Psychology,* 1971, *77*, 302–312.

Schimmel, R. J., & Knobil, E. Insulin, free fatty acids, and stimulation of hepatic gluconeogenesis during fasting. *American Journal of Physiology,* 1970, *218*, 1540–1547.

Schmitt, M. Influences of hepatic portal receptors on hypothalamic feeding and satiety centers. *American Journal of Physiology,* 1973, *225*, 1089–1095.

Sclafani, A., & Grossman, S. P. Hyperphagia produced by knife cuts between the medial and lateral hypothalamus in the rat. *Physiology and Behavior,* 1969, *4*, 533–537.

Seyffert, W. A., Jr., & Madison, L. L. Physiologic effects of metabolic fuels on carbohydrate metabolism. I. Acute effect of elevation of plasma free fatty acids on hepatic glucose output, peripheral glucose utilization, serum insulin, and plasma glucagon levels. *Diabetes,* 1967, *16*, 765–776.

Sherwin, R. S., Hendler, R. G., & Felig, P. Effect of ketone infusions on amino acid and nitrogen metabolism in man. *Journal of Clinical Investigation,* 1975, *55*, 1382–1390.

Shimazu, T. Glycogen synthetase activity in liver: Regulation by the autonomic nerves. *Science,* 1967, *156*, 1256–1257.

Shimazu, T., & Fukuda, A. Increased activities of glycogenolytic enzymes in liver after splanchnic-nerve stimulation. *Science,* 1965, *150*, 1607–1608.

Shimazu, T., Fukuda, A., & Ban, T. Reciprocal influences of the ventromedial and lateral hypothalamic nuclei on blood glucose level and liver glycogen content. *Nature,* 1966, *210*, 1178–1179.

Sims, E. A. H., Horton, E. S., & Salans, L. B. Inducible metabolic abnormalities during development of obesity. *Annual Review of Medicine,* 1971, *22*, 235–250.

Singh, D. Effects of preoperative training on food-motivated behavior of hypothalamic hyperphagic rats. *Journal of Comparative and Physiological Psychology,* 1973, *84*, 47–52.

Singh, D. Role of preoperative experience on reaction to quinine taste in hypothalamic hyperphagic rats. *Journal of Comparative and Physiological Psychology,* 1974, *86*, 674–678.

Smith, G. P., & Epstein, A. N. Increased feeding in response to decreased glucose utilization in the rat and monkey. *American Journal of Physiology,* 1969, *217*, 1083–1087.

Smith, G. P., & Gibbs, J. Cholecystokinin and satiety: Theoretic and therapeutic implications. In D. Novin, W. Wyricka, & G. Bray, (Eds.), *Hunger: Basic mechanisms and clinical implications.* New York: Raven Press, 1976.

Smith, G. P., Gibbs, J., Strohmayer, A. J., Root, A. W., & Stokes, P. E. Effect of 2-deoxy-D-glucose on insulin response to glucose in intact and adrenalectomized monkeys. *Endocrinology,* 1973, *92*, 750–754.

Snowdon, C. T. Gastrointestinal sensory and motor control of food intake. *Journal of Comparative and Physiological Psychology,* 1970, *71*, 68–76.

Sokoloff, L. Metabolism of ketone bodies by the brain. *Annual Review of Medicine,* 1973, *24*, 271–280.

Steffens, A. B. The influence of insulin injections and infusions on eating and blood glucose level in the rat. *Physiology and Behavior,* 1969, *4*, 823–828. (a)

Steffens, A. B. Rapid absorption of glucose in the intestinal tract of the rat after ingestion of a meal. *Physiology and Behavior,* 1969, *4*, 829–832. (b)

Steffens, A. B. Plasma insulin content in relation to blood glucose level and meal pattern in the normal and hypothalamic hyperphagic rat. *Physiology and Behavior,* 1970, *5*, 147–151.

Steffens, A. B. Influence of reversible obesity on eating behavior, blood glucose, and insulin in the rat. *American Journal of Physiology,* 1975, *228*, 1738–1744.

Steffens, A. B., Mogenson, G. J., & Stevenson, J. A. F. Blood glucose, insulin, and free fatty acids after stimulation and lesions of the hypothalamus. *American Journal of Physiology,* 1972, *222*, 1446–1452.

Stellar, E. The physiology of motivation. *Psychological Review,* 1954, *61*, 5–22.

Stevenson, J. A. F. Mechanisms in the control of food and water intake. *Annals of the New York Academy of Sciences,* 1969, *157*, 1069–1083.

Stricker, E. M. Drinking by rats after lateral hypothalamic lesions: A new look at the lateral hypothalamic syndrome. *Journal of Comparative and Physiological Psychology,* 1976, *90*, 127–143.

Stricker, E. M., Friedman, M. I., & Zigmond, M. J. Glucoregulatory feeding by rats after intraventricular 6-hydroxydopamine or lateral hypothalamic lesions. *Science,* 1975, *189*, 895–897.

Stricker, E. M., & Zigmond, M. J. Effects on homeostasis of intraventricular injection of 6-hydroxydopamine in rats. *Journal of Comparative and Physiological Psychology,* 1974, *86*, 973–994.

Stricker, E. M., & Zigmond, M. J. Recovery of function following damage to central catecholamine-containing neurons: A neurochemical model for the lateral hypothalamic syndrome. In J. M. Sprague & A. N. Epstein (Eds.), *Progress in psychobiology and physiological psychology* (Vol. 6). New York: Academic Press, 1976.

Strubbe, J. H., & Steffens, A. B. Rapid insulin release after ingestion of a meal in the unanesthetized rat. *American Journal of Physiology,* 1975, *229*, 1019–1022.

Stunkard, A. Satiety is a conditioned reflex. *Psychosomatic Medicine,* 1975, *37*, 383–387.

Sullivan, A. C., & Triscari, J. Possible interrelationship between metabolic flux and appetite. In D. Novin, W. Wyricka, & G. Bray (Eds.), *Hunger:*

Basic mechanisms and clinical implications. New York: Raven Press, 1976.

Tannenbaum, G. A., Paxinos, G., & Bindra, D. Metabolic and endocrine aspects of the ventromedial hypothalamic syndrome in the rat. *Journal of Comparative and Physiological Psychology,* 1974, *86,* 404–413.

Teitelbaum, P. Sensory control of hypothalamic hyperphagia. *Journal of Comparative and Physiological Psychology,* 1955, *48,* 156–163.

Teitelbaum, P. Random and food-directed activity in hyperphagic and normal rats. *Journal of Comparative and Physiological Psychology,* 1957, *50,* 486–490.

Teitelbaum, P. Disturbances in feeding and drinking behavior after hypothalamic lesions. In M. R. Jones (Ed.), *Nebraska Symposium on Motivation* (Vol. 9). Lincoln: University of Nebraska Press, 1961.

Teitelbaum, P., & Epstein, A. N. The lateral hypothalamic syndrome: Recovery of feeding and drinking after lateral hypothalamic lesions. *Psychological Review,* 1962, *69,* 74–90.

Teitelbaum, P., & Stellar, E. Recovery from the failure to eat produced by hypothalamic lesions. *Science,* 1954, *120,* 894–895.

Teitelbaum, P., & Wolgin, D. L. Neurotransmitters and the regulation of food intake. *Progress in Brain Research,* 1975, *42,* 235–249.

Tepperman, J., & Tepperman, H. M. Effects of antecedent food intake pattern on hepatic lipogenesis. *American Journal of Physiology,* 1958, *193,* 55–64.

Tepperman, J., & Tepperman, H. M. Gluconeogenesis, lipogenesis and the Sherringtonian metaphor. *Federation Proceedings,* 1970, *29,* 1284–1293.

Thomas, D. W., & Mayer, J. Meal taking and regulation of food intake by normal and hypothalamic hyperphagic rats. *Journal of Comparative and Physiological Psychology,* 1968, *66,* 642–653.

Toates, F. M., & Booth, D. A. Control of food intake by energy supply. *Nature,* 1974, *251,* 710–711.

Ugolev, A. M., & Kassil, V. G. [Physiology of the appetite.] *Uspekhi Sovremennoi biologii,* 1961, *51,* 352–368.

Unger, R. H. Alpha- and beta-cell interrelationships in health and disease. *Metabolism,* 1974, *23,* 581–593.

Ungerstedt, U. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. *Acta Physiologica Scandinavica,* 1971, *82*(Suppl. 367), 95–122.

Van Harken, D. R., Dixon, C. W., & Heimberg, M. Hepatic lipid metabolism in experimental diabetes. V. The effect of concentration of oleate on metabolism of triglycerides and on ketogenesis. *Journal of Biological Chemistry,* 1969, *244,* 2278–2285.

Vilberg, T. R., & Beatty, W. W. Behavioral changes following VMH lesions in rats with controlled insulin levels. *Pharmacology, Biochemistry and Behavior,* 1975, *3,* 377–384.

Wayner, M. J., Cott, A., Millner, J., and Tartaglione, R. Loss of 2-deoxy-D-glucose induced eating in recovered lateral rats. *Physiology and Behavior,* 1971, *7,* 881–884.

Wick, A. N., Drury, D. R., & Morita, T. N. 2-Deoxyglucose—A metabolic block for glucose. *Proceedings of the Society for Experimental Biology and Medicine,* 1955, *89,* 579–582.

Wick, A. N., Drury, D. R., Nakada, H. I., & Wolfe, J. B. Localization of the primary metabolic block produced by 2-deoxyglucose. *Journal of Biological Chemistry,* 1957, *224,* 963–969.

Wieland, O. Ketogenesis and its regulation. *Advances in Metabolic Disorders,* 1968, *3,* 1–47.

Wiepkema, P. R., Alingh Prins, A. J., & Steffens, A. B. Gastrointestinal food transport in relation to meal occurrence in rats. *Physiology and Behavior,* 1972, *9,* 759–763.

Williams, D. R., & Teitelbaum, P. Some observations on the starvation resulting from lateral hypothalamic lesions. *Journal of Comparative and Physiological Psychology,* 1959, *52,* 458–465.

Winegrad, A. I. Adipose tissue in diabetes. In A. E. Renold & G. F. Cahill, Jr. (Eds.), *Handbook of physiology* (Vol. 5). Baltimore: Williams & Wilkins, 1965.

Wolf, L. L., & Hainsworth, F. R. Temporal patterning of feeding by hummingbirds. *Animal Behaviour,* in press.

Woods, S. C., Decke, E., & Vasselli, J. R. Metabolic hormones and regulation of body weight. *Psychological Review,* 1974, *81,* 26–43.

York, D. A., & Bray, G. A. Genetic obesity in rats. II. The effect of food restriction on the metabolism of adipose tissue. *Metabolism,* 1973, *22,* 443–454.

Zigmond, M. J., & Stricker, E. M. Deficits in feeding behavior after intraventricular injection of 6-hydroxydopamine in rats. *Science,* 1972, *177,* 1211–1214.

Zigmond, M. J., & Stricker, E. M. Recovery of feeding and drinking by rats after intraventricular 6-hydroxydopamine or lateral hypothalamic lesions. *Science,* 1973, *182,* 717–720.

Zucker, L. M. Efficiency of energy utilization by the Zucker hereditarily obese rat "fatty." *Proceedings of the Society for Experimental Biology and Medicine,* 1975, *148,* 498–500.

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